A 3-year-old girl is brought to the office after developing fever and a sore throat. The patient recently entered day care, and similar symptoms have been reported in several of the other children. Physical examination shows exudative pharyngitis and enlarged anterior cervical lymph nodes. A rapid antigen detection test confirms the diagnosis of streptococcal throat infection. Her condition resolves with antibiotic therapy. Several weeks later, she is re-exposed to *Streptococcus pyogenes*. The bacteria penetrating beyond the surface epithelium are immediately coated with preformed IgG antibodies. Which of the following substances acts in the most similar manner to IgG antibodies to facilitate phagocytosis?

A. 5-Hydroxyicosatetraenoic acid
B. Complement C3b
C. Complement C5a
D. Immunoglobulin M
E. Leukotriene B4
F. L-selectin

Submit

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- A. 5-Hydroxyicosatetraenoic acid (0%)
- ✓ B. Complement C3b (78%)
- C. Complement C5a (8%)
- D. Immunoglobulin M (9%)
- E. Leukotriene B4 (1%)
- F. L-selectin (1%)

Omitted
Correct answer
B

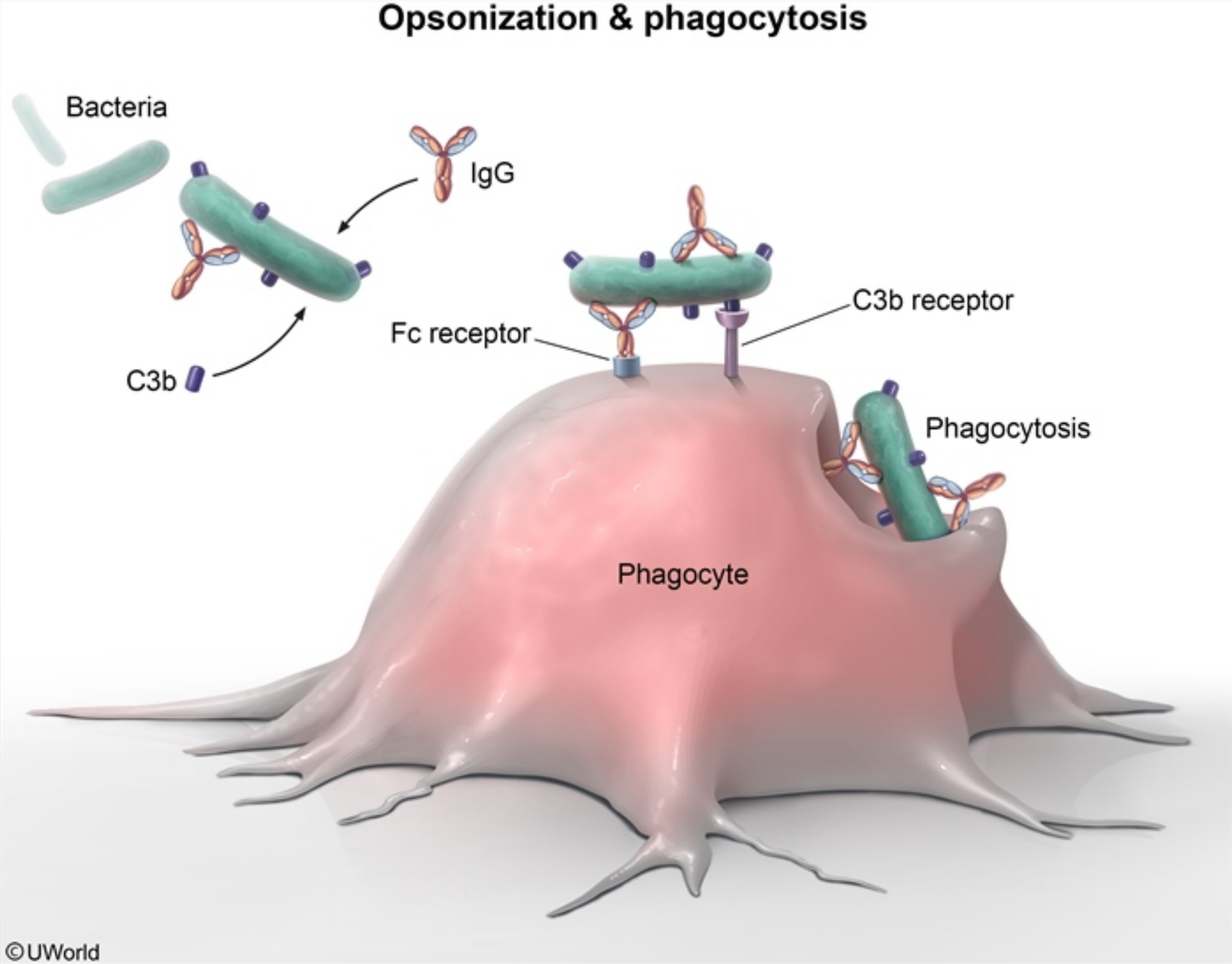
78%
Answered correctly

10 mins, 49 secs
Time Spent

04/11/2020
Last Updated

Explanation

Opsonization & phagocytosis



Opsonization occurs when host proteins such as immunoglobulins or complement bind to the surface of foreign cells (eg, bacteria) to promote **phagocytosis**. The most important opsonins (coating proteins) are **immunoglobulin (Ig) G** and **complement C3b**, but mannose-binding lectin

Opsonization occurs when host proteins such as immunoglobulins or complement bind to the surface of foreign cells (eg, bacteria) to promote **phagocytosis**. The most important opsonins (coating proteins) are **immunoglobulin (Ig) G** and **complement C3b**, but mannose-binding lectin and C-reactive protein can also opsonize cells. After opsonins are bound to the cell surface, they act as a handle for receptors on phagocytes (eg, Fc receptors, C3b receptors) to grasp, allowing the phagocytes to more easily engulf the foreign cell.

The importance of C3 is demonstrated by the fact that all 3 complement pathways (lectin, classical, and alternative) converge on it, resulting in cleavage into C3a and C3b. C3a helps recruit phagocytic cells and induce inflammation. C3b, in addition to acting as an opsonin, can bind to C3b convertase and form C5 convertase, ultimately triggering the membrane attack complex.

(Choice A) 5-Hydroxyicosatetraenoic acid (5-HETE) is produced by a variety of immune cells and serves as a leukotriene and lipoxin precursor. It also causes neutrophil and macrophage chemotaxis and neutrophil degranulation.

(Choice C) Complement C5a can enhance phagocytosis by macrophages, but it does so by binding to receptors on the phagocytes and stimulating them directly, not by coating the foreign cells. It also is a potent chemotactic agent, drawing more neutrophils and monocytes to the site of inflammation.

(Choice D) Although IgM can be a potent stimulator of C3b opsonization via activation of the complement cascade, there are no receptors on macrophages for the Fc portion of IgM and it does not directly enhance phagocytosis (unlike IgG).

(Choice E) Leukotriene B4 is a chemotactic agent that increases the ability of leukocytes to cross from the serum into the tissues as part of an inflammatory response.

(Choice F) L-selectin is an adhesion molecule that aids entry of lymphocytes from the blood into lymphoid tissue and margination of neutrophils during inflammatory responses.

Educational objective:
Opsonization occurs when host proteins such as immunoglobulins or complement bind to foreign cells such as bacteria and coat the surface, enhancing phagocytosis. The most important opsonins (coating proteins) are immunoglobulin G and complement C3b.

References

- Neutrophils and macrophages work in concert as inducers and effectors of adaptive immunity against extracellular and intracellular microbial

(Choice A) 5-Hydroxyicosatetraenoic acid (5-HETE) is produced by a variety of immune cells and serves as a leukotriene and lipoxin precursor. It also causes neutrophil and macrophage chemotaxis and neutrophil degranulation.

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References

- Neutrophils and macrophages work in concert as inducers and effectors of adaptive immunity against extracellular and intracellular microbial pathogens.
- Complement System Part II: Role in Immunity.

Immunology	Allergy & Immunology	Pharyngitis
Subject	System	Topic

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A 3-year-old boy is being evaluated for persistent diarrhea. Although the patient seemed healthy at his 12-month well child visit, since then he has experienced 4 episodes of otitis media and 3 episodes of pneumococcal pneumonia. He was at the 50th percentile for weight and height at 12 months but is now at the 25th percentile for height and 10th percentile for weight. The patient is referred for upper gastrointestinal endoscopy, and *Giardia lamblia* is isolated from duodenal aspirates. Further workup shows very low serum levels of all immunoglobulin types. Flow cytometry of this patient's peripheral blood is most likely to show a near absence of cells bearing which of the following markers?

- A. CD4
- B. CD8
- C. CD15
- D. CD16
- E. CD19

Submit

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A. CD4 (17%)

B. CD8 (4%)

C. CD15 (3%)

D. CD16 (3%)

✓ E. CD19 (70%)

Omitted
Correct answer
E

70%
Answered correctly

02 secs
Time Spent

07/01/2020
Last Updated

Explanation

This patient's recurrent sinopulmonary infections, *Giardia lamblia* gastroenteritis, failure to thrive, and low immunoglobulin levels are suggestive of **X-linked agammaglobulinemia** (XLA). In this condition, a mutation in the Bruton tyrosine kinase gene causes failure of bone marrow pre-B cells to develop into mature B cells, a step necessary for B cells to leave the bone marrow and enter the peripheral circulation.

Patients with XLA have **low or absent B cells** in the peripheral blood and lymphoid tissues and **pan-hypogammaglobulinemia** (ie, very low IgG,

This patient's recurrent sinopulmonary infections, *Giardia lamblia* gastroenteritis, failure to thrive, and low immunoglobulin levels are suggestive of **X-linked agammaglobulinemia** (XLA). In this condition, a mutation in the Bruton tyrosine kinase gene causes failure of bone marrow pre-B cells to develop into mature B cells, a step necessary for B cells to leave the bone marrow and enter the peripheral circulation.

Patients with XLA have **low or absent B cells** in the peripheral blood and lymphoid tissues and **pan-hypogammaglobulinemia** (ie, very low IgG, IgM, and IgA). As a result, they are at increased risk of infection with pyogenic (encapsulated) bacteria. Patients also have increased susceptibility to certain viral and parasitic infections, such as enteroviruses and *Giardia lamblia*, due to the absence of opsonizing and neutralizing antibodies.

Flow cytometry can be used to assess the number of circulating B cells by using fluorescent tags that bind to **specific B cell surface proteins** such as **CD19, CD20, and CD21**.

(Choices A and B) CD4 is a helper T cell surface marker, and CD8 is a cytotoxic T cell surface marker. Both B cells and T cells can be deficient in patients with certain forms of severe combined immunodeficiency. However, these patients typically have failure to thrive, persistent mucosal candidiasis, and severe infections with opportunistic organisms (eg, *Pneumocystis*) at a much younger age (~6 months).

(Choice C) CD15 is a cell surface protein present on granulocytes. It is also present on nearly all Reed-Sternberg cells and is therefore a cytologic marker useful in the diagnosis of Hodgkin lymphoma.

(Choice D) CD16 is a low-affinity Fc receptor found on the surface of natural killer cells, neutrophils, and macrophages.

Educational objective:
X-linked agammaglobulinemia is characterized by low or absent circulating mature B cells (ie, $CD19^+$, $CD20^+$, $CD21^+$ cells) and pan-hypogammaglobulinemia. Affected patients have increased susceptibility to pyogenic bacteria, enteroviruses, and *Giardia lamblia* due to the absence of opsonizing and neutralizing antibodies.

Immunology	Allergy & Immunology	X-linked agammaglobulinemia
Subject	System	Topic

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A 5-year-old girl is brought to the office for evaluation of a persistent cough. The patient has had a productive cough daily for the past month. History includes recurrent episodes of otitis media despite bilateral ear tube placement, numerous lower respiratory tract infections, and occasional ulcerative skin lesions. Laboratory evaluation shows normal levels of total B and T cells and serum immunoglobulin. Genetic testing reveals a mutation in the *TAP1* gene, which encodes a protein involved in the transport of cytosolic molecules into the endoplasmic reticulum. Which of the following processes is most likely to be impaired by this mutation?

- A. B cell differentiation into plasma cells
- B. Cytotoxic T cell activation by MHC class I molecules
- C. Destruction of phagocytized organisms
- D. MHC class II molecule expression on B cells
- E. Migration and extravasation of neutrophils

Submit

A 5-year-old girl is brought to the office for evaluation of a persistent cough. The patient has had a productive cough daily for the past month. History includes recurrent episodes of otitis media despite bilateral ear tube placement, numerous lower respiratory tract infections, and occasional ulcerative skin lesions. Laboratory evaluation shows normal levels of total B and T cells and serum immunoglobulin. Genetic testing reveals a mutation in the *TAP1* gene, which encodes a protein involved in the transport of cytosolic molecules into the endoplasmic reticulum. Which of the following processes is most likely to be impaired by this mutation?

- A. B cell differentiation into plasma cells (3%)
- ✓ B. Cytotoxic T cell activation by MHC class I molecules (50%)
- C. Destruction of phagocytized organisms (15%)
- D. MHC class II molecule expression on B cells (23%)
- E. Migration and extravasation of neutrophils (6%)

Omitted
Correct answer
B

50%
Answered correctly

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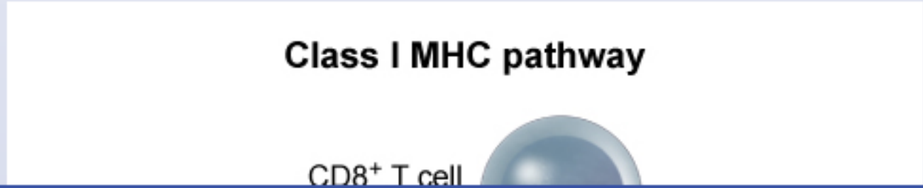
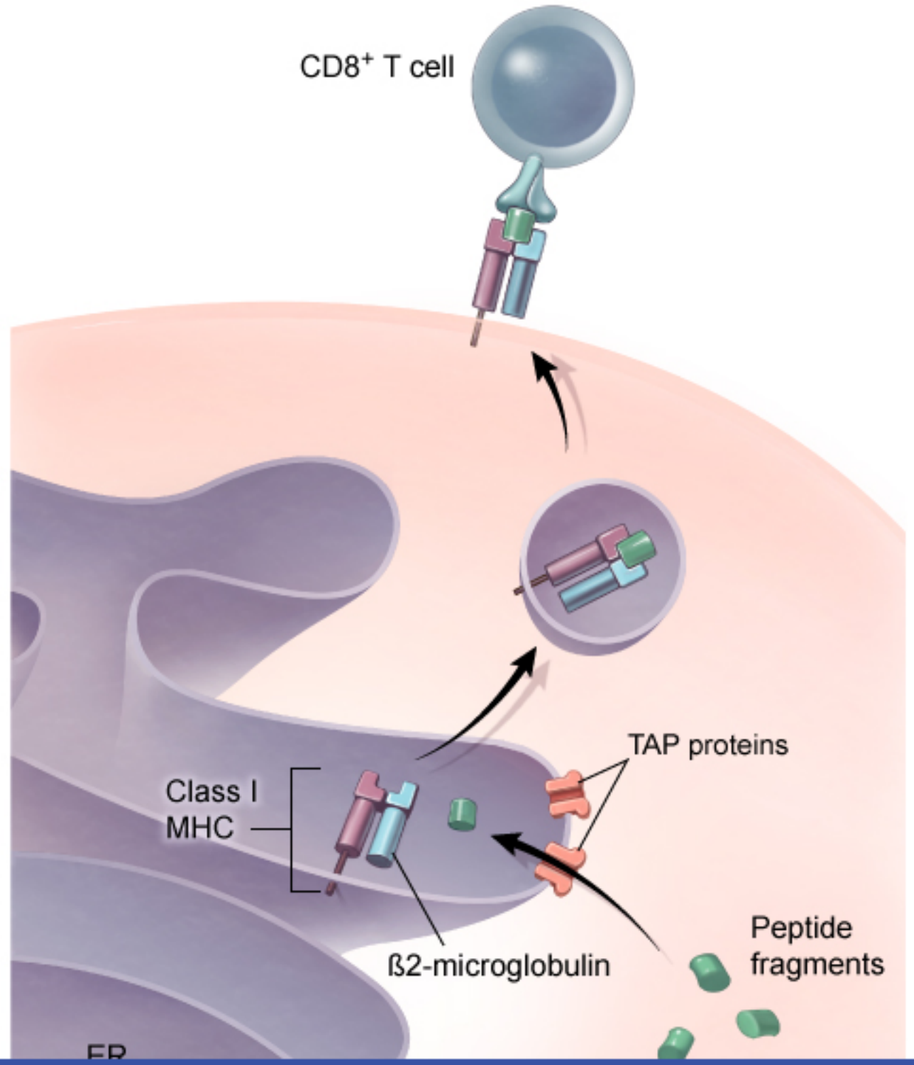
Time Spent

06/16/2020
Last Updated

Explanation



Class I MHC pathway



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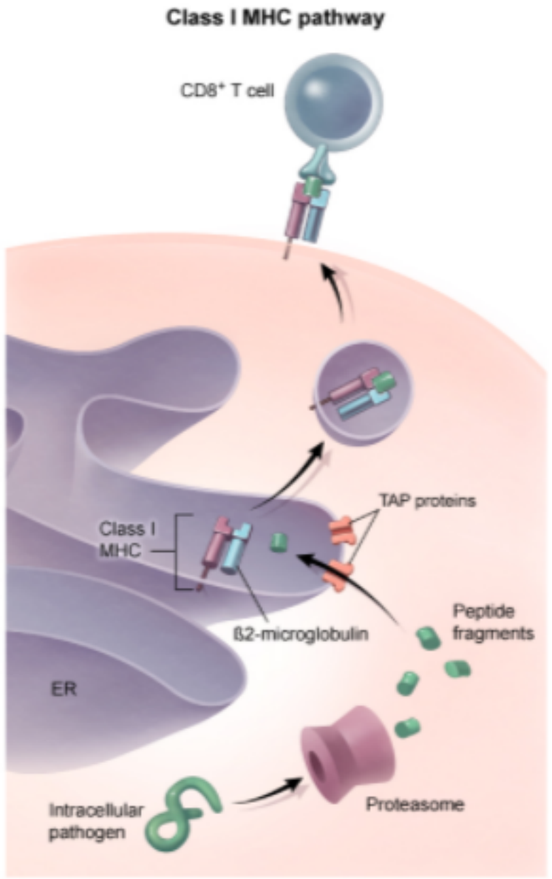

ER = endoplasmic reticulum; MHC = major histocompatibility complex; TAP = transporter associated with antigen processing.

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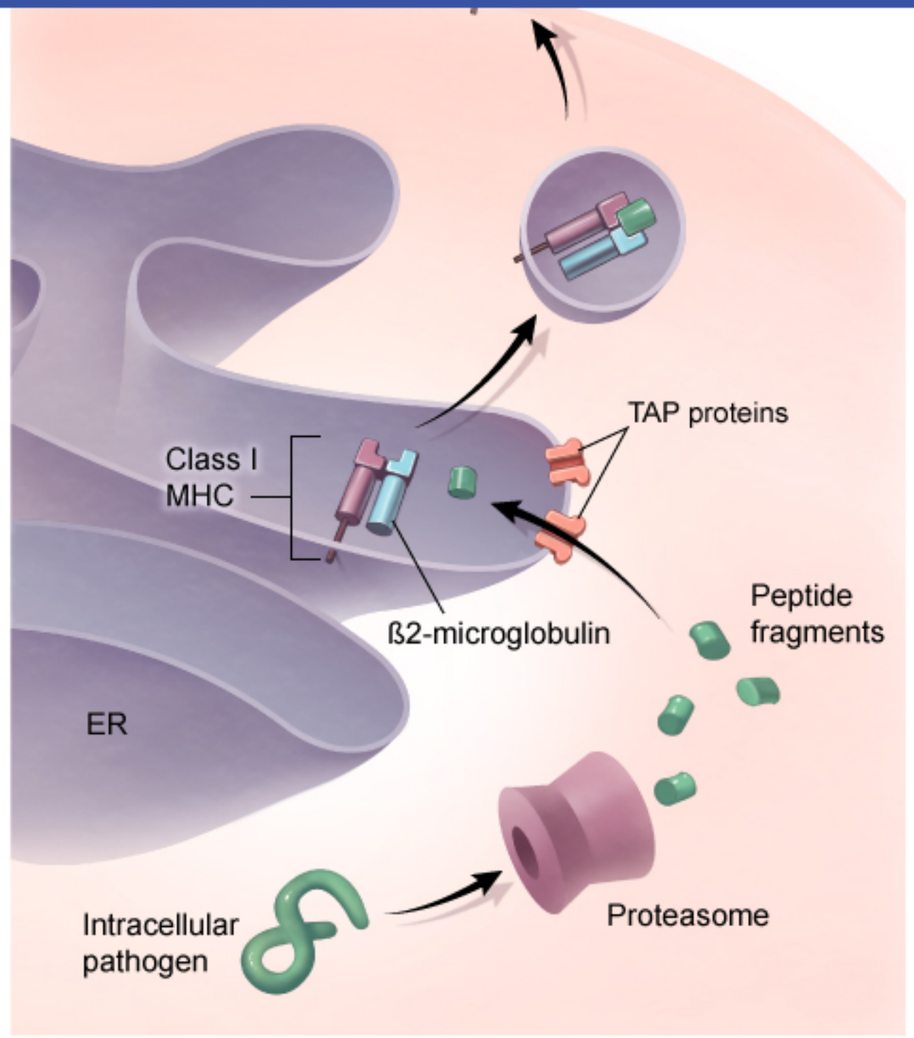

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Transporter associated with antigen processing **(TAP) proteins** are transmembrane proteins necessary for the presentation of cytosolic antigens on major histocompatibility complex (MHC) molecules. When cellular proteins (or pathogen-derived proteins) are degraded by proteasomes, some of the resulting peptide fragments are transported into the endoplasmic reticulum by TAP proteins and loaded onto **MHC class I molecules**. The MHC class I–peptide complexes then translocate to the cell surface where they can activate cytotoxic T cells through interaction with T cell receptors and CD8 coreceptors.

The activated T cells clonally expand and kill damaged or infected cells by releasing cytotoxins (eg, perforin, granzyme) that induce **apoptosis**. Genetic mutations (eg, *TAP1*) affecting MHC class I–peptide complex expression (eg, bare lymphocyte syndrome type I) are rare but can cause ulcerative, granulomatous skin lesions and frequent respiratory infections despite normal lymphocyte and immunoglobulin levels.

(Choice A) B cell differentiation into plasma cells is impaired in common variable immune deficiency, a multifactorial disorder without a clearly defined genetic basis. A decrease in the overall production of immunoglobulin results in recurrent respiratory tract and gastrointestinal infections.

(Choice C) Chronic granulomatous disease is characterized by impaired destruction of phagocytized organisms in neutrophils due to a mutation (usually X linked) that causes decreased production of NADPH oxidase. The lack of superoxide production needed for the oxidative burst in neutrophils results in recurrent, severe bacterial and fungal infections in an infant or toddler.

(Choice D) MHC class II molecules are expressed on antigen-presenting cells (eg, macrophages, B cells) after phagocytized proteins are degraded within lysosomes and added to MHC class II molecules. T helper ($CD4^+$) cells are activated by the MHC class II–peptide complex and coordinate the adaptive immune response. TAP does not play a role in antigen loading of MHC class II molecules.

(Choice E) Migration and extravasation of neutrophils is impaired in leukocyte adhesion deficiency due to a mutation in integrins necessary for the adhesion of immune cells to blood vessel walls. Without this adhesion, neutrophils are unable to leave blood vessels to follow chemotactic signals, resulting in delayed separation of the umbilical cord, recurrent bacterial infections, neutrophilia, and absent pus formation.

Educational objective:
Transporter associated with antigen processing (TAP) proteins are necessary for loading of cytoplasmic (eg, viral) proteins onto major histocompatibility complex (MHC) class I molecules. The MHC class I–peptide complex can then activate $CD8^+$ cytotoxic T cells through interaction with the T cell receptor and CD8 coreceptor.

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Immunology	General Principles	Major histocompatibility class
Subject	System	Topic

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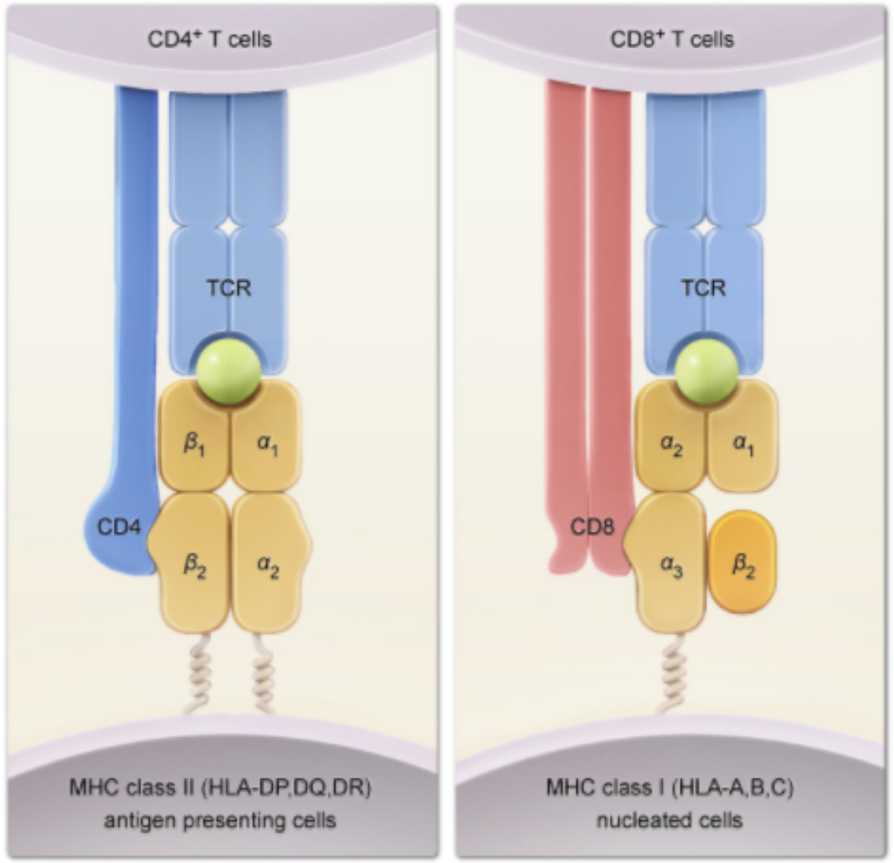
MHC-TCR interaction



MHC = major histocompatibility complex; TCR = t-cell receptor.

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receptors and CD8 coreceptors.

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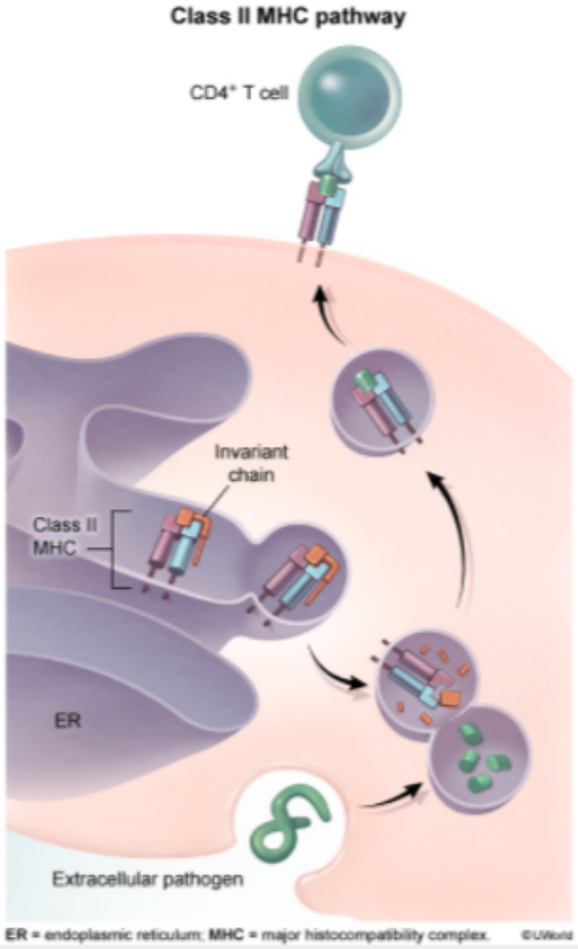

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A 5-year-old child is brought to the emergency department by his parents for right arm pain. The patient reports that he was playing hide and seek outside and felt a sharp pain on his arm while hiding in some thick bushes. His parents suspect that something had stung him. Physical examination shows an edematous and erythematous plaque with mild central pallor. A residual stinger, located central to the lesion, is readily extracted. The physical examination is otherwise not significant. Which of the following substances is most likely directly responsible for the skin findings observed in this patient?

- A. C3b
- B. IL-2
- C. Histamine
- D. Lysozyme
- E. TNF-α

Submit

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- A. C3b (2%)
- B. IL-2 (4%)
- ✓ C. Histamine (86%)
- D. Lysozyme (1%)
- E. TNF-α (5%)

Omitted
Correct answer
C

86%
Answered correctly

02 secs
Time Spent

07/02/2020
Last Updated

Explanation

This child is experiencing a local allergic reaction (**type I hypersensitivity**) to an insect sting. The cutaneous findings are consistent with a wheal-and-flare reaction, an erythematous papule or plaque often with central pallor (wheal) and peripheral erythema (flare).

During initial allergen exposure, a patient predisposed to an allergic response will undergo antibody class switching from IgM to **IgE antibodies** specific for the allergen. IgE produced by B lymphocytes and plasma cells then binds to high-affinity IgE Fc receptors on **basophils** and **mast**

Explanation

This child is experiencing a local allergic reaction (**type I hypersensitivity**) to an insect sting. The cutaneous findings are consistent with a wheal-and-flare reaction, an erythematous papule or plaque often with central pallor (wheal) and peripheral erythema (flare).

During initial allergen exposure, a patient predisposed to an allergic response will undergo antibody class switching from IgM to **IgE antibodies** specific for the allergen. IgE produced by B lymphocytes and plasma cells then binds to high-affinity IgE Fc receptors on **basophils** and **mast cells**. Re-exposure to the allergen results in cross-linking of bound IgE antibodies with subsequent degranulation and release of inflammatory mediators (eg, **histamine**, proteases [tryptase], leukotrienes, prostaglandins). Localized vasodilation and increased vascular permeability result in the characteristic wheal-and-flare lesions. In severe cases, widespread release of these agents can also cause systemic vasodilation, bronchoconstriction, and massive fluid shifts, leading to anaphylactic shock and potentially death.

(Choice A) C3b, the larger subunit produced by cleavage of complement component 3, binds to pathogens and enhances phagocytosis. The C3b component of immune complexes formed by type III hypersensitivity reactions can also bind to CR1 receptors on erythrocytes, facilitating their clearance in the liver and spleen.

(Choice B) IL-2 is a cytokine produced by T_H1 lymphocytes that increases proliferation and activity of helper, cytotoxic, and regulatory T cells as well as NK cells. T_H1 cells are responsible for inducing macrophage and cytotoxic T lymphocyte-mediated (type IV) inflammatory reactions. In contrast, IL-4 is responsible for driving the production of T_H2 cells, which promote antibody-mediated (humoral) immunity and facilitate type I hypersensitivity.

(Choice D) Lysozyme is an antimicrobial enzyme found in specific granules of neutrophils and bodily secretions (tears, mucus). Lysozyme functions by hydrolyzing bonds within the peptidoglycan cell walls of bacterial organisms. It is an important component of innate immunity, not hypersensitivity reactions.

(Choice E) TNF-α is a proinflammatory cytokine produced by macrophages and T cells that induces and maintains granuloma formation (important for host defense against tuberculosis). It also plays a pathogenic role in inflammatory conditions such as rheumatoid arthritis, psoriasis, and inflammatory bowel disease. TNF-α may be elevated in type IV (delayed type) hypersensitivity, but not type I.

Educational objective:
Wheal-and-flare lesions usually result from allergic (type I hypersensitivity) reactions. On initial exposure, an allergen (eg, insect venom) promotes

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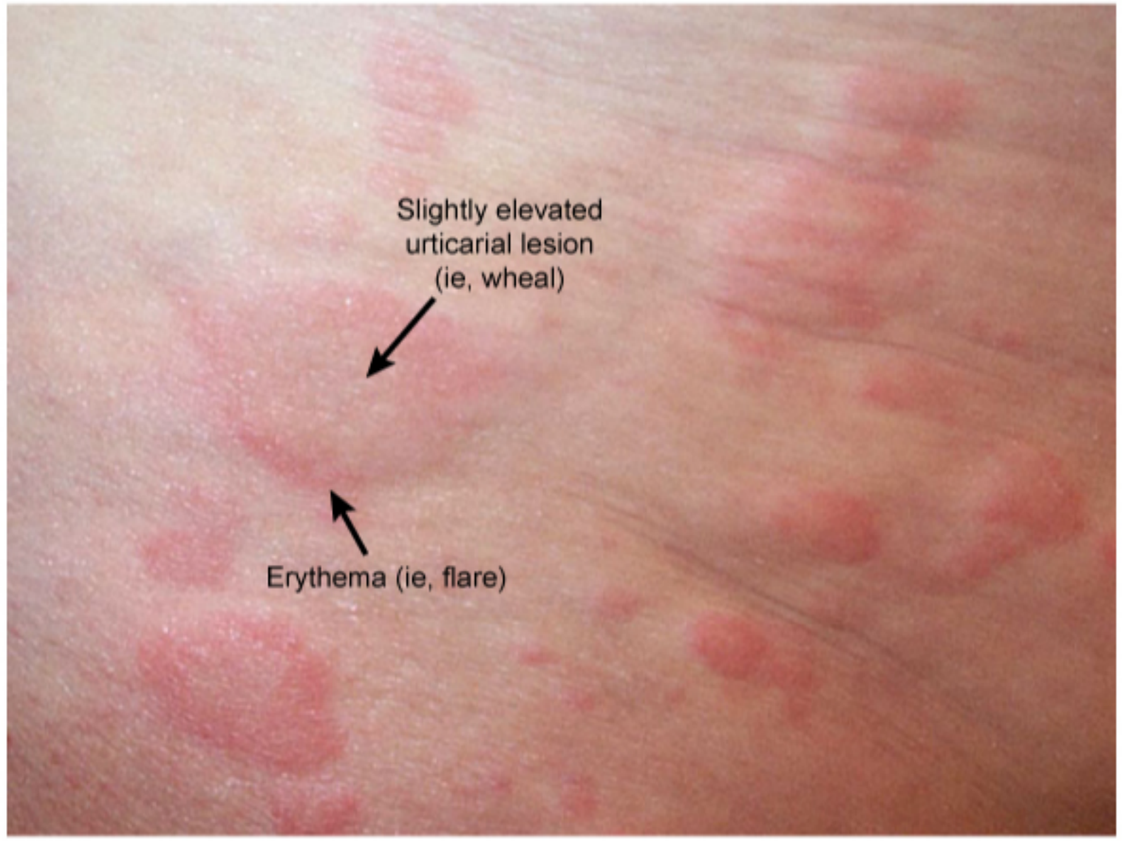
Explanation

Exhibit Display

Wheal and flare



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Educational objective:
Wheal-and-flare lesions usually result from allergic (type I hypersensitivity) reactions. On initial exposure, an allergen (eg, insect venom) promotes antibody class switching to IgE. Subsequent exposure promotes cross-linking of IgE on basophils and mast cells, resulting in degranulation and release of multiple vasoactive mediators, including histamine.

Immunology	Allergy & Immunology	Hypersensitivity reactions
Subject	System	Topic

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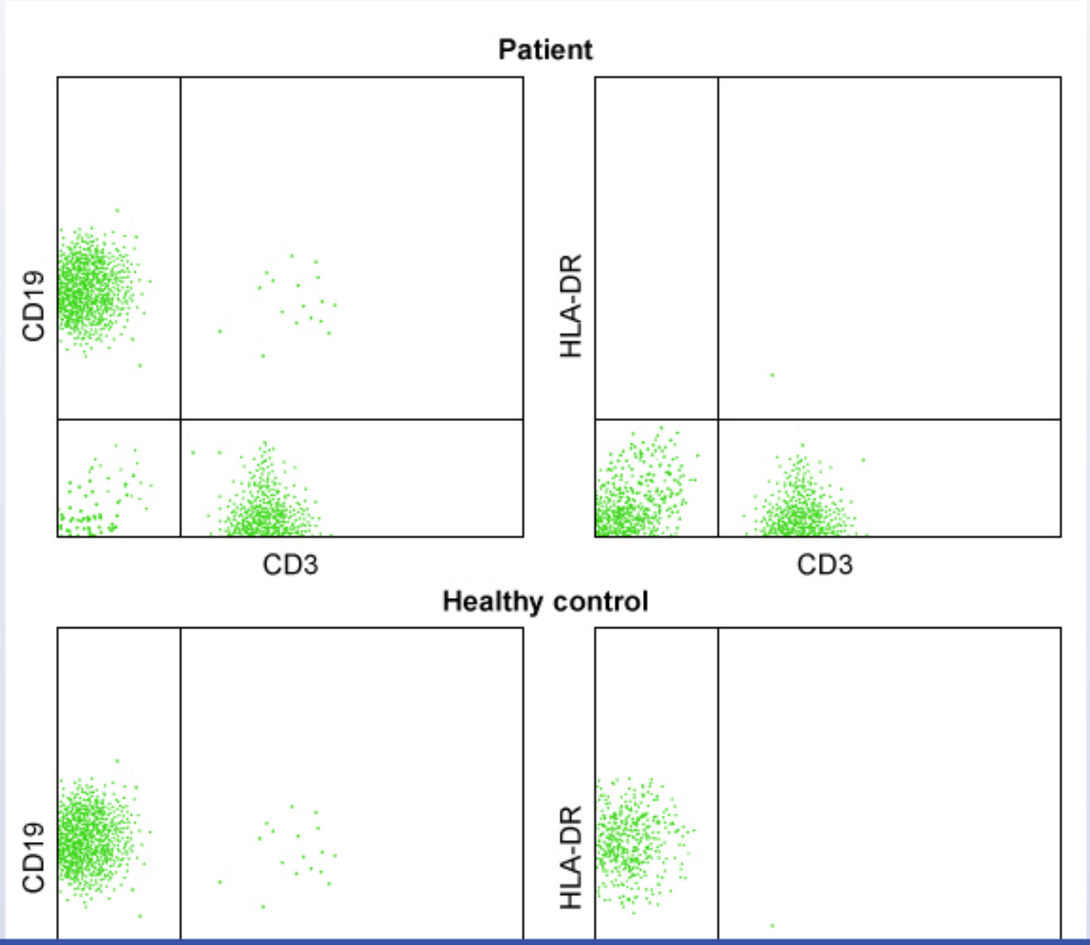
A 10-month-old boy is hospitalized for respiratory distress due to *Pneumocystis jiroveci* pneumonia. The patient has had repeated episodes of otitis media and thrush; weight is below the 5th percentile. Laboratory evaluation reveals normal levels of circulating B and T cells with low levels of all immunoglobulins. Genetic testing reveals a rare autosomal recessive mutation resulting in a defect in the regulation of human leukocyte antigen gene transcription. Flow cytometry of the patient's peripheral blood compared with a healthy control is shown in the illustration below:



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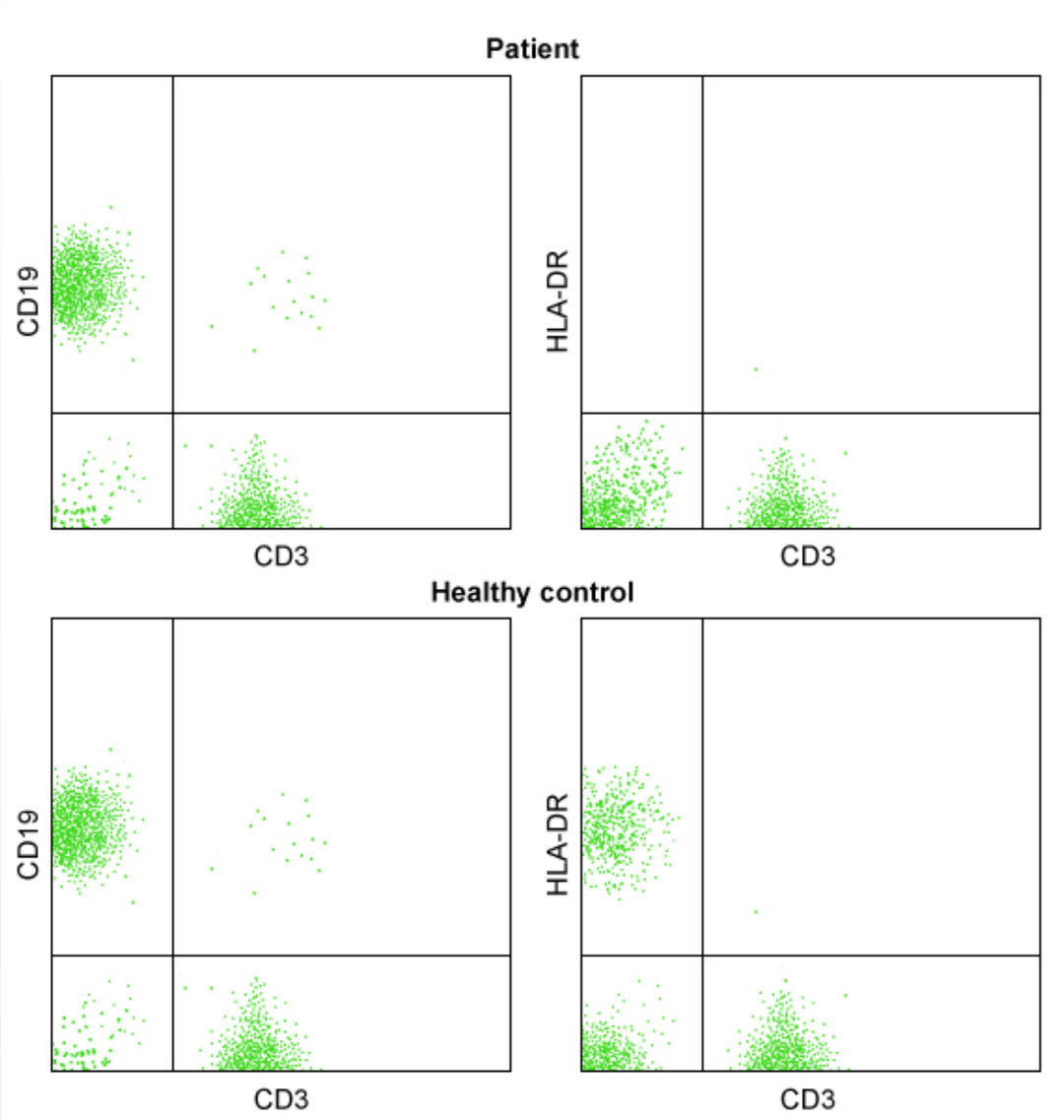

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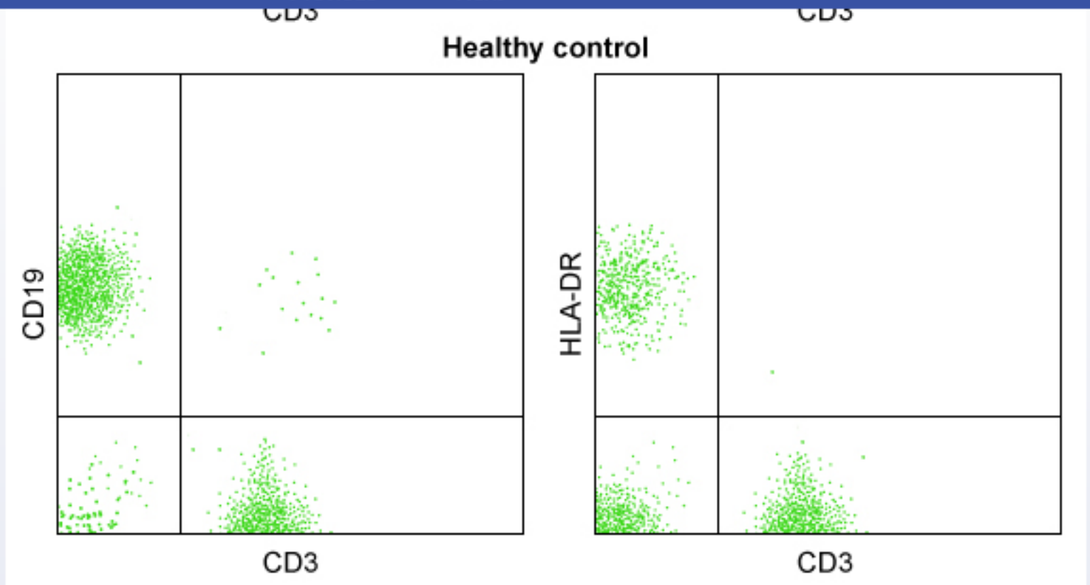

Which of the following processes is most likely to be impaired by this patient's mutation?

A. Development of pharyngeal pouches

B. Capability of activated $CD4^+$ T cells to express CD40L

C. Maturation of pro-B cells into pre-B cells

D. Presentation of antigens processed in lysosomes

E. Transport of cytosolic proteins into the endoplasmic reticulum

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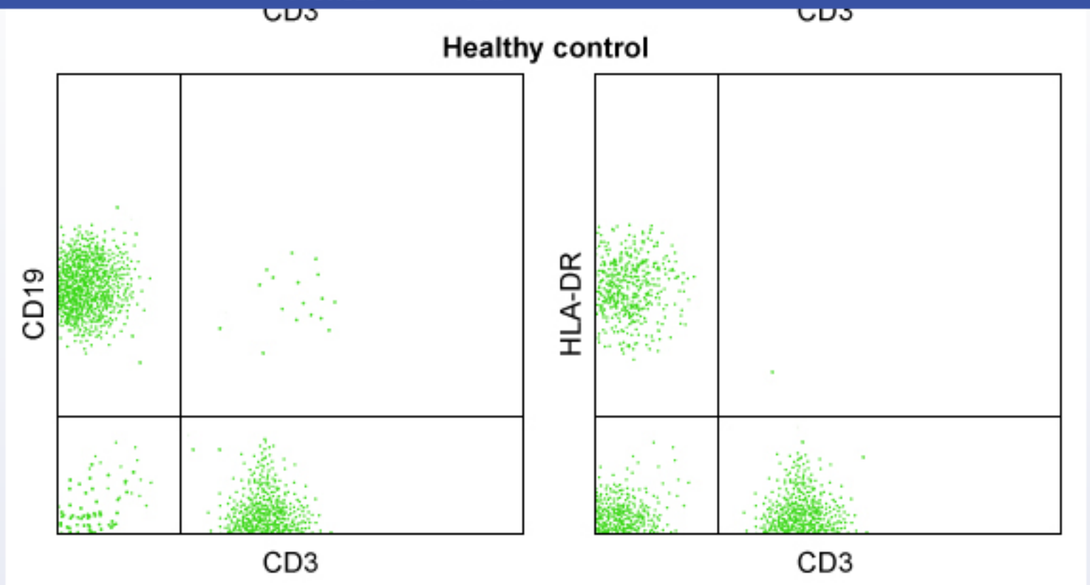

Which of the following processes is most likely to be impaired by this patient's mutation?

A. Development of pharyngeal pouches (2%)

B. Capability of activated CD4⁺ T cells to express CD40L (23%)

C. Maturation of pro-B cells into pre-B cells (15%)

✓ D. Presentation of antigens processed in lysosomes (54%)

E. Transport of cytosolic proteins into the endoplasmic reticulum (4%)

Omitted
Correct answer

54%
Answered correctly

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Last Updated

Explanation

This patient's flow cytometry shows normal numbers of $CD3^+$ cells (reflecting circulating T cells) and $CD19^+$ cells (reflecting circulating B cells). However, an absence of $HLA\text{-}DR^+$ cells indicates defective expression of major histocompatibility complex (MHC) class II molecules. The human leukocyte antigen (HLA) genes encode MHC molecules expressed on the cell surface for antigen presentation. There are 6 major HLA loci:

- *HLA-DP*, *HLA-DQ*, and ***HLA-DR*** genes encode **MHC class II** molecules, which are expressed on **antigen-presenting cells** (eg, B cells, macrophages) after an extracellular antigen has been loaded onto the MHC class II molecule in an acidified **lysosome**.
- *HLA-A*, *HLA-B*, and *HLA-C* genes encode MHC class I molecules, which are expressed on nucleated cells after a cytosolic antigen has been transported into the endoplasmic reticulum and loaded onto the MHC class I molecule **(Choice E)**.

Because expression of the MHC class II–peptide complex is necessary for activation of B and T cells, its absence (eg, bare lymphocyte syndrome type II) causes a form of severe combined immunodeficiency.

(Choice A) DiGeorge syndrome is an autosomal dominant disorder caused by the deletion of a segment of chromosome 22 (*22q11.2*). Failed development of the thymus results in T cell deficiency, which would be evident by a reduction in $CD3^+$ cells on flow cytometry.

(Choice B) CD40 ligand (CD40L) is expressed on activated T helper cells and interacts with CD40 on B cells to promote immunoglobulin class-switching. Impaired CD40L expression can result in hyperimmunoglobulin M syndrome (ie, high IgM levels and low/absent circulating IgG, IgA, and IgE). Although this patient's mutation impairs activation of T cells, his $CD4^+$ T cells would still be capable of expressing CD40L upon activation.

(Choice C) Maturation of pro-B cells into pre-B cells with resulting expression of B cell–specific surface markers (eg, CD19, CD40) is dependent on signal transduction by Bruton tyrosine kinases. A mutation in the *BTK* gene causes X-linked agammaglobulinemia, which is characterized by hypogammaglobulinemia and recurrent infections after maternal IgG is depleted (~3 months of age). Flow cytometry would show a marked decrease in $CD19^+$ cells.

Educational objective:
Major histocompatibility complex (MHC) class II molecules are encoded by the *HLA-DP*, *HLA-DQ*, and *HLA-DR* genes and present extracellular antigens processed in acidified lysosomes by antigen-presenting cells (eg, B cells, macrophages). Absence of MHC class II expression impairs

macrophages) after an extracellular antigen has been loaded onto the MHC class II molecule in an acidified **lysosome**.

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Major histocompatibility complex (MHC) class II molecules are encoded by the *HLA-DP*, *HLA-DQ*, and *HLA-DR* genes and present extracellular antigens processed in acidified lysosomes by antigen-presenting cells (eg, B cells, macrophages). Absence of MHC class II expression impairs activation of B and T cells, resulting in a form of severe combined immunodeficiency.

Immunology	General Principles	Major histocompatibility class
Subject	System	Topic

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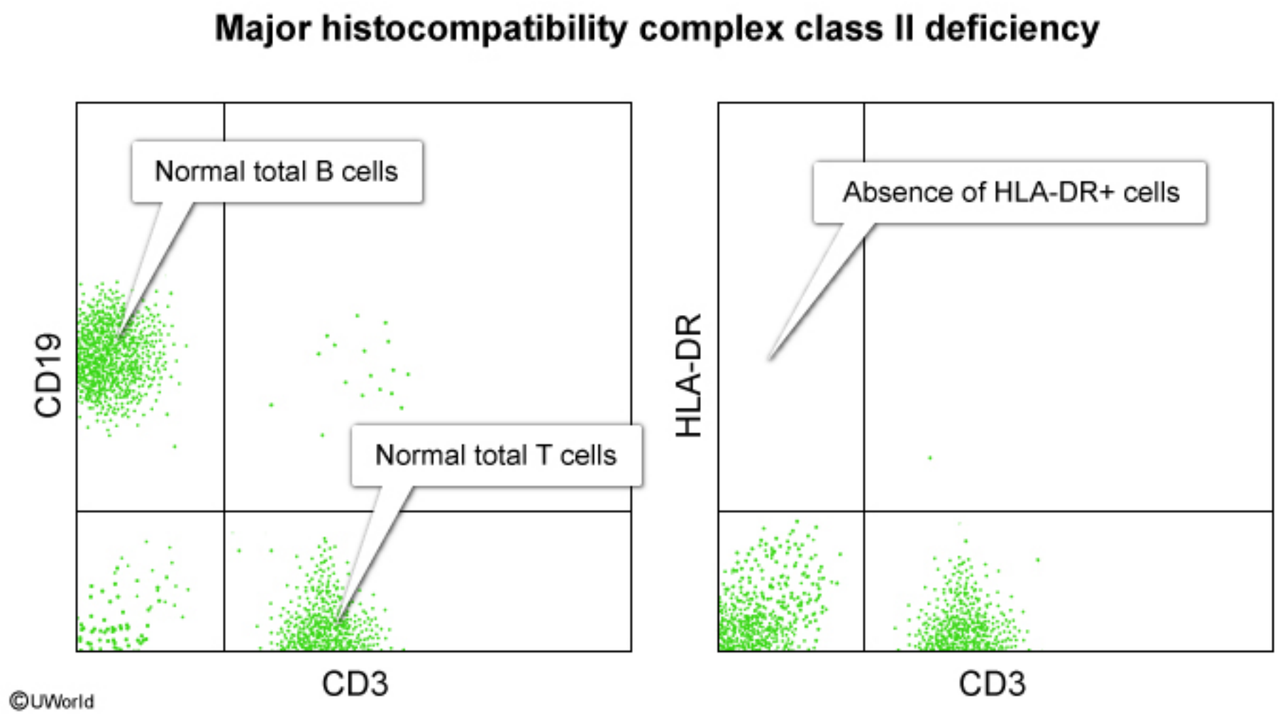

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antigens processed in acidified lysosomes by antigen presenting cells (eg, B cells, macrophages). Absence of MHC class II expression impairs

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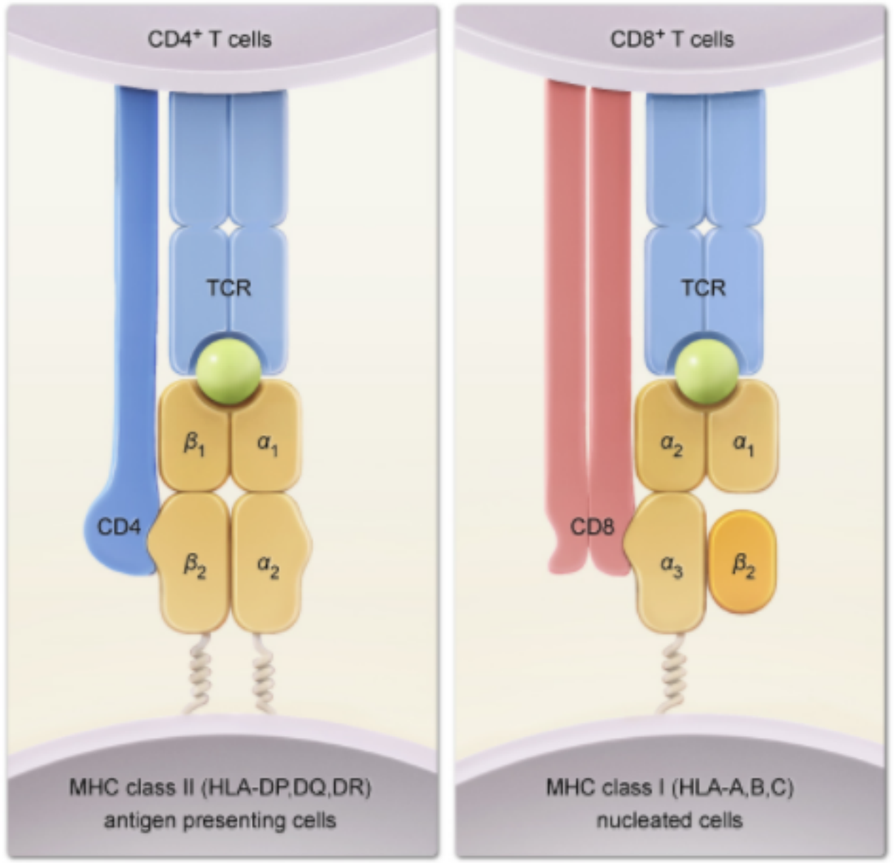
Explanation

Exhibit Display

MHC-TCR interaction



MHC = major histocompatibility complex; TCR = t-cell receptor.

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antigens processed in acidified lysosomes by antigen presenting cells (eg, B cells, macrophages). Absence of MHC class II expression impairs

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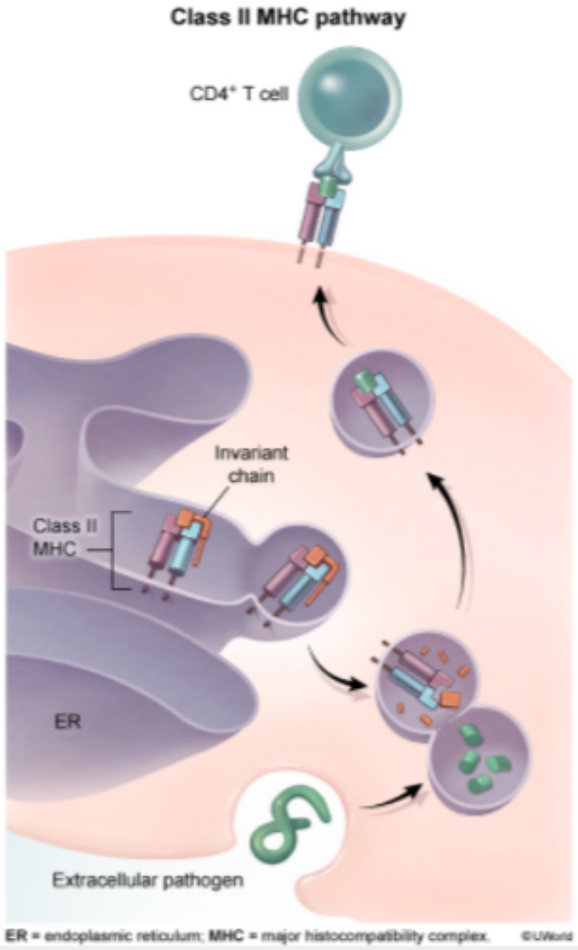

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antigens processed in acidified lysosomes by antigen presenting cells (eg, B cells, macrophages). Absence of MHC class II expression impairs

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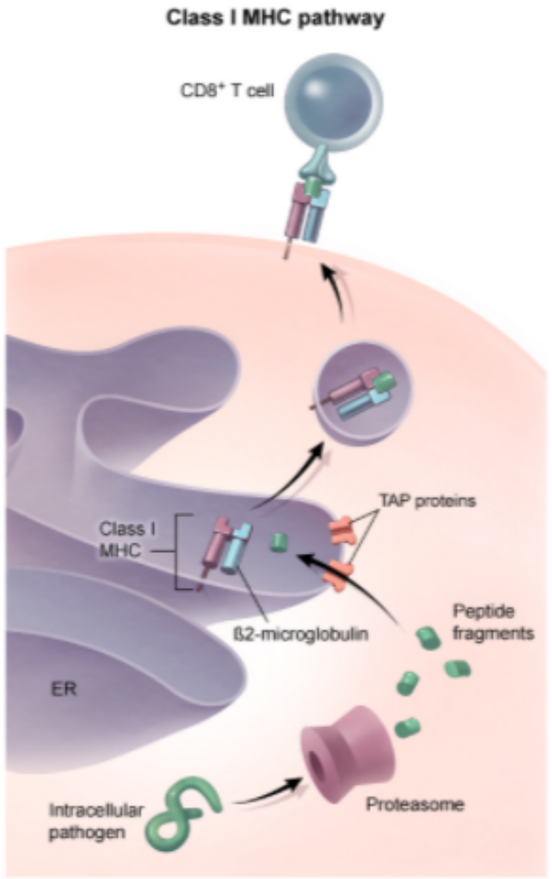

ER = endoplasmic reticulum; MHC = major histocompatibility complex; TAP = transporter associated with antigen processing.

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antigens processed in acidified lysosomes by antigen presenting cells (eg, B cells, macrophages). Absence of MHC class II expression impairs

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Explanation

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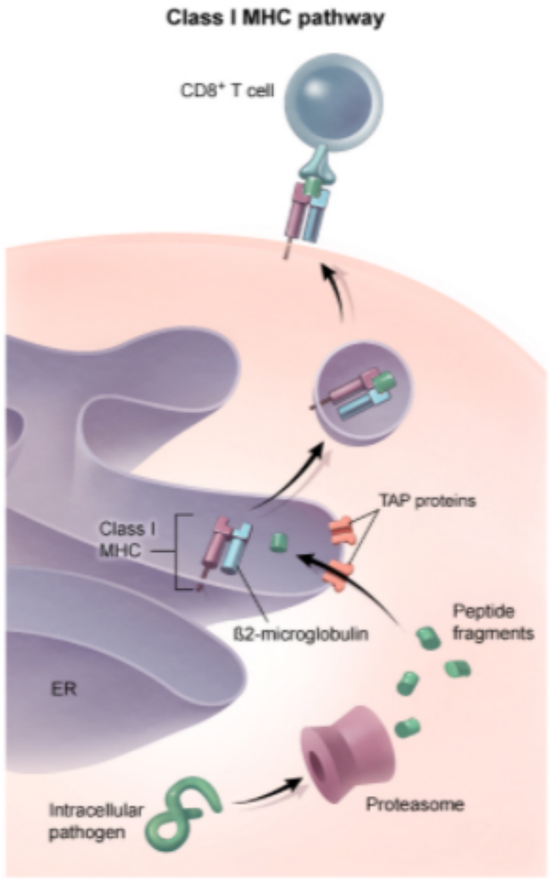

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Immunology	General Principles	Major histocompatibility class
Subject	System	Topic

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The following vignette applies to the next **2** items. The items in the set must be answered in sequential order. Once you click **Proceed to Next Item**, you will not be able to add or change an answer.

A 13-month-old boy is brought to the emergency department due to cough and increased work of breathing. On physical examination, he is tachypneic and has perioral cyanosis. A chest radiograph shows bilateral interstitial opacities. Review of his medical records shows a recurrent history of otitis media, pneumonia, and thrush as well as chronic diarrhea and failure to thrive. The patient is admitted to the hospital and undergoes bronchoscopy. Analysis of the bronchoalveolar lavage fluid shows *Pneumocystis jirovecii*.

Item 1 of 2

Which of the following is the most likely diagnosis?

- A. Agammaglobulinemia
- B. Chronic granulomatous disease
- C. Cystic fibrosis
- D. Primary ciliary dyskinesia
- E. Severe combined immune deficiency
- F. Terminal complement deficiency

Submit

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Item 1 of 2

Which of the following is the most likely diagnosis?

- A. Agammaglobulinemia (7%)
- B. Chronic granulomatous disease (3%)
- C. Cystic fibrosis (7%)
- D. Primary ciliary dyskinesia (1%)
- ✓ E. Severe combined immune deficiency (79%)
- F. Terminal complement deficiency (0%)

Omitted
Correct answer
E

79%
Answered correctly

02 secs
Time Spent

03/03/2020
Last Updated

Severe combined immunodeficiency	
Etiology	• Gene defect leading to failure of T cell development • B cell dysfunction due to absent T cells
Inheritance	• X-linked recessive • Autosomal recessive
Clinical features	• Recurrent, severe viral, fungal, or opportunistic (ie, *Pneumocystis*) infections • Failure to thrive • Chronic diarrhea
Treatment	• Stem cell transplant

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Severe combined immunodeficiency (SCID) is characterized by defective **T cell development** and **B cell dysfunction**. SCID can be caused by mutations in several different genes and may be inherited in an X-linked or autosomal recessive pattern. The absence of T cells causes severe defects in cellular immunity. Affected patients are at high risk for infections with viruses, fungi, and opportunistic pathogens (eg, *Pneumocystis jirovecii*). The loss of helper T cell function leads to B cell dysfunction (ie, deficient humoral/antibody-mediated immunity) and, therefore, recurrent sinopulmonary bacterial infections (eg, pneumonia, otitis media). In addition to infection, **chronic diarrhea** and **failure to thrive** in infancy are typical.

SCID is included in routine newborn screening in the United States. Laboratory findings of SCID include lymphopenia and hypogammaglobulinemia. Stem cell transplant is the only treatment and should be performed as early as possible. Congenital HIV infection can present similarly and should be considered in a patient with recurrent infections and failure to thrive.

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(Choice A) Agammaglobulinemia is an isolated B cell defect that manifests with recurrent sinopulmonary bacterial infections. Infection with *Pneumocystis jirovecii* is not seen in isolated B cell defects.

(Choice B) Chronic granulomatous disease is a disorder of phagocyte dysfunction due to defective NADPH oxidase. This leads to bacterial (eg, *Staphylococcus aureus*) and fungal (eg, *Aspergillus*) infections, such as abscesses, pneumonia, and osteomyelitis.

(Choice C) Cystic fibrosis is an autosomal recessive disease caused by dysregulation of a chloride channel found in multiple organs (eg, lung, pancreas). Thick airway secretions and pancreatic insufficiency lead to recurrent respiratory infections and chronic diarrhea, respectively. *Pneumocystis* and thrush would not be expected.

(Choice D) Primary ciliary dyskinesia is an autosomal recessive disease that results in poor mucociliary clearance in the respiratory tract, middle ear, and reproductive organs. Affected patients have recurrent sinopulmonary infections in childhood and decreased fertility in adulthood. Viral or opportunistic infections are not seen.

(Choice F) Terminal complement deficiency (any of C5-C9) prevents formation of the membrane attack complex and results in increased susceptibility to infections by *Neisseria*.

Educational objective:

Severe combined immunodeficiency is caused by a genetic defect in T cell development, leading to loss of both cellular and humoral immunity.

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Educational objective:
Severe combined immunodeficiency is caused by a genetic defect in T cell development, leading to loss of both cellular and humoral immunity. Patients present in infancy with recurrent bacterial, viral, fungal, and opportunistic infections as well as failure to thrive and chronic diarrhea.

References

- Severe combined immunodeficiency (SCID): from molecular basis to clinical management.
- Evaluation of primary immunodeficiency disease in children.

Immunology	Allergy & Immunology	Primary immunodeficiency disorder
Subject	System	Topic

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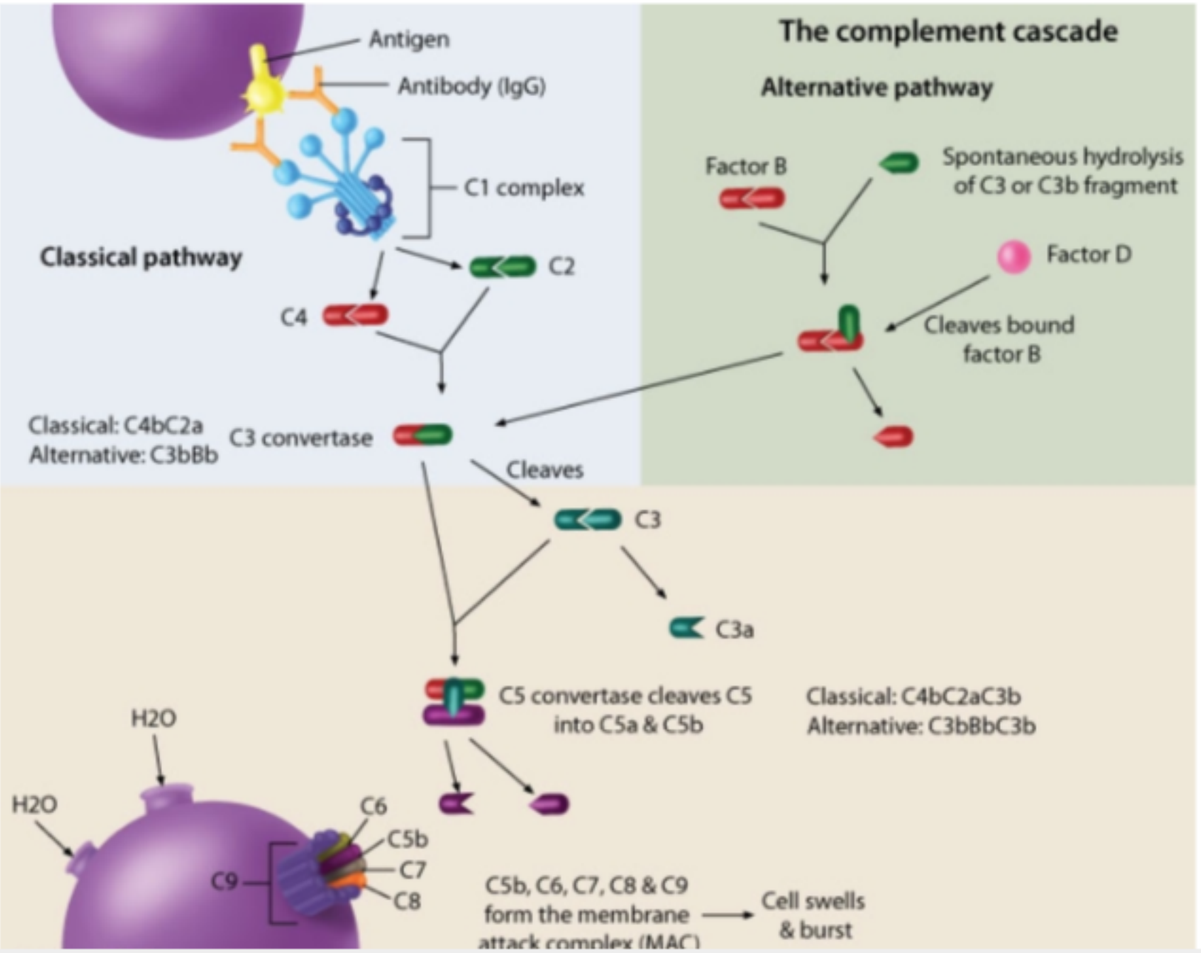

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Immunology | Allergy & Immunology | Primary immunodeficiency disorder

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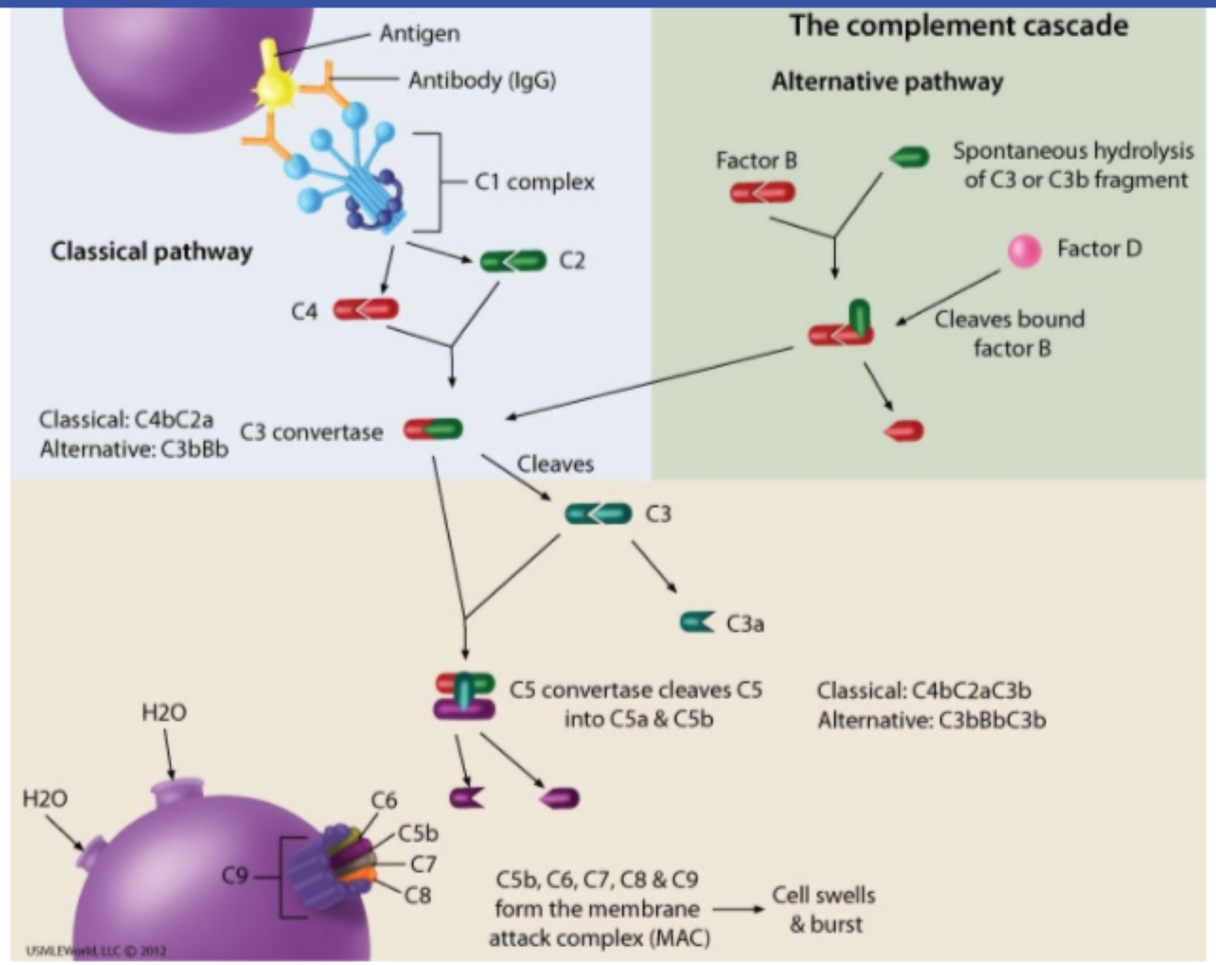

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Immunology | Allergy & Immunology | Primary immunodeficiency disorder

Item 2 of 2

Once the patient recovers from the acute illness, *Candida* antigen injection into his skin reveals no signs of inflammation in 48 hours. The same test performed in his mother produces 12 mm of skin induration within 48 hours. Which of the following cells are directly involved in the response observed in the mother?

- A. B lymphocytes and CD4+ T lymphocytes
- B. B lymphocytes and CD8+ T lymphocytes
- C. CD4+ T lymphocytes and fibroblasts
- D. CD4+ T lymphocytes and macrophages
- E. CD8+ T lymphocytes and eosinophils

Submit

Item 2 of 2

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A. B lymphocytes and CD4+ T lymphocytes (12%)
B. B lymphocytes and CD8+ T lymphocytes (9%)
C. CD4+ T lymphocytes and fibroblasts (1%)
✓ D. CD4+ T lymphocytes and macrophages (65%)
E. CD8+ T lymphocytes and eosinophils (11%)

Omitted
Correct answer
D

65%
Answered correctly

03 secs
Time Spent

03/03/2020
Last Updated

Explanation

The candidal antigen skin test is used to determine the presence of cellular, or T cell-mediated, immunity through the detection of a **delayed-type hypersensitivity reaction** (type IV). The key cells involved are **macrophages, CD4⁺ helper T cells**, and **CD8⁺ cytotoxic T cells**. Macrophages present the injected candida antigen to CD4⁺ helper T cells. In response, CD4⁺ T cells secrete cytokines that recruit CD8⁺ T cells to the area and produce the characteristic signs of induration and erythema. CD4⁺ and CD8⁺ T cells both produce interferon gamma, which stimulates phagocytosis of *Candida* by the macrophages. Failure to generate a response is referred to as **anergy**, which is expected in SCID patients who

Explanation

The candidal antigen skin test is used to determine the presence of cellular, or T cell-mediated, immunity through the detection of a **delayed-type hypersensitivity reaction** (type IV). The key cells involved are **macrophages, $CD4^+$ helper T cells**, and **$CD8^+$ cytotoxic T cells**. Macrophages present the injected candida antigen to $CD4^+$ helper T cells. In response, $CD4^+$ T cells secrete cytokines that recruit $CD8^+$ T cells to the area and produce the characteristic signs of induration and erythema. $CD4^+$ and $CD8^+$ T cells both produce interferon gamma, which stimulates phagocytosis of *Candida* by the macrophages. Failure to generate a response is referred to as **anergy**, which is expected in SCID patients who are deficient in both T and B cell lines. Virtually all people are sensitized to *Candida*, and so the candidal skin test can be used as a positive control for other antigens (eg, tuberculin skin testing).

(Choices A and B) B lymphocytes are a component of humoral, or antibody-mediated, immunity. Antibodies play a prominent role in type II (eg, drug-induced hemolytic anemia) and type III (eg, serum sickness) hypersensitivity reactions but not in type IV reactions.

(Choices C and E) Eosinophils and fibroblasts are not involved in type IV hypersensitivity reactions. Eosinophils are part of the innate immune system and are increased with atopic or parasitic diseases. Fibroblasts are found in connective tissue and are integral in wound healing through the production of extracellular matrix and collagen.

Educational objective:
The candidal antigen skin test assesses the activity of T cell-mediated immunity through the recruitment of macrophages and $CD4^+$ and $CD8^+$ T lymphocytes in a type IV hypersensitivity reaction. Anergy, or failure to respond to candida antigen testing, is typical in patients with severe combined immunodeficiency.

References

- Recent advances in understanding the pathophysiology of primary T cell immunodeficiencies.

Immunology	Allergy & Immunology	Hypersensitivity reactions
Subject	System	Topic

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References

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Immunology	Allergy & Immunology	Hypersensitivity reactions
Subject	System	Topic

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A 68-year-old man comes to the emergency department with a 2-day history of fever, chills, and productive cough. His temperature is 38.9 C (102 F), blood pressure is 108/52 mm Hg, pulse is 102/min, and respirations are 26/min. Crackles and bronchial breath sounds are heard over the right lower lung. There is dullness to percussion over the same area. Chest x-ray reveals right lower lobe consolidation and a right-sided pleural effusion. The patient is started on the appropriate treatment, and a diagnostic thoracentesis is performed that shows an uncomplicated parapneumonic effusion. When a sterile sample of the inflammatory exudate is experimentally introduced into normal human tissue, rapid neutrophil locomotion is observed. Which of the following components of the exudate is most likely responsible for this observed effect?

- A. Bradykinin
- B. C4a
- C. IFN-γ
- D. IL-4
- E. Leukotriene B_4
- F. Thromboxane A_2

Submit

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- A. Bradykinin (1%)
- B. C4a (8%)
- C. IFN-γ (9%)
- D. IL-4 (7%)
- ✓ E. Leukotriene B_4 (71%)
- F. Thromboxane A_2 (0%)

Omitted
Correct answer
E

71%
Answered correctly

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05/19/2020
Last Updated

Explanation

Arachidonic acid metabolic pathways

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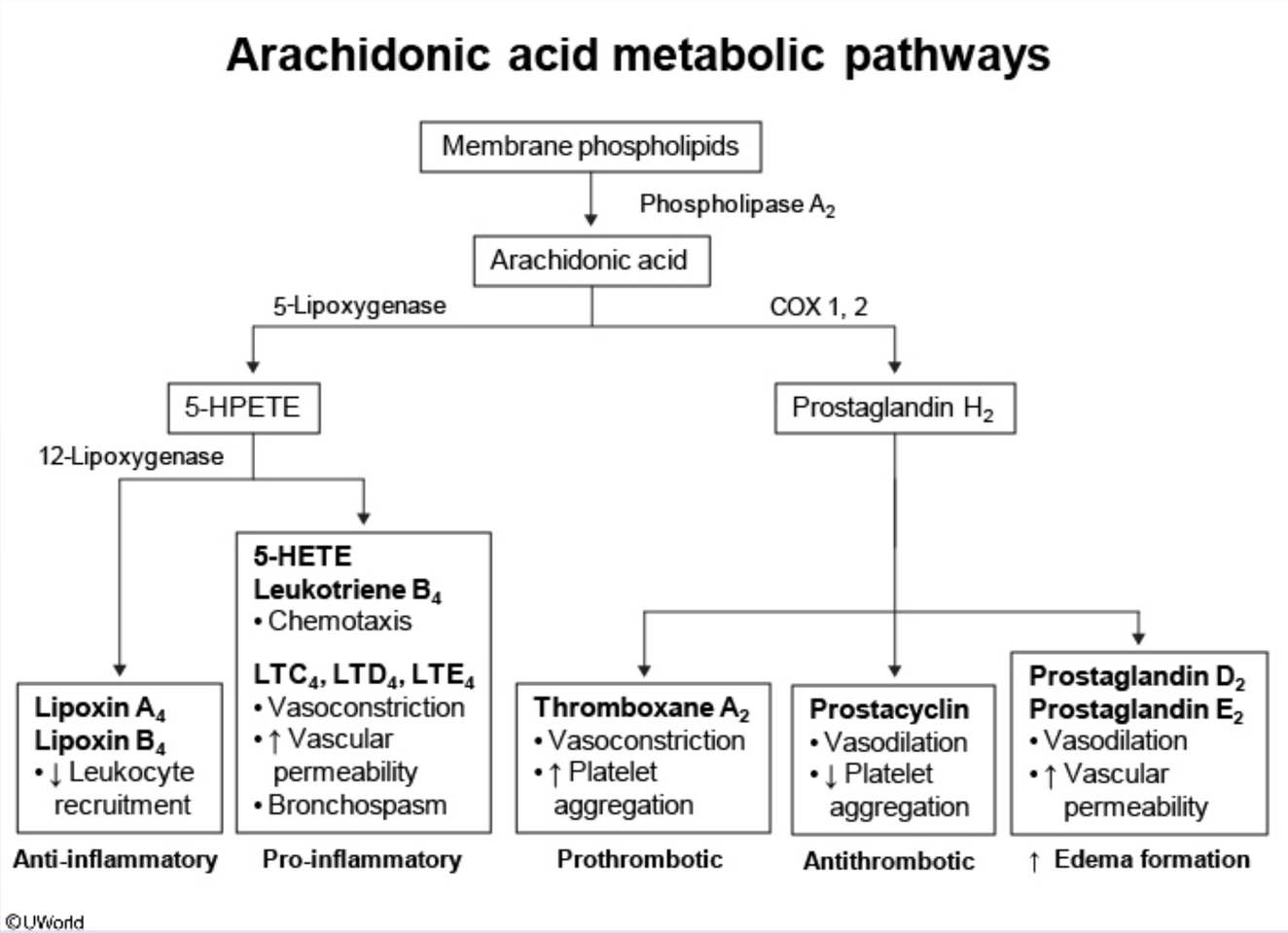

Parapneumonic effusions occur frequently in bacterial pneumonia as a result of **exudative** fluid accumulation within the pleural space. Infections and other forms of inflammatory tissue injury cause increased vascular permeability, leading to the formation of protein-rich exudates that contain a variety of biologically active substances. Under the influence of inflammatory stimuli, cell membrane phospholipids release arachidonic acid, a precursor to the eicosanoid inflammatory mediators (eg, prostanoids, leukotrienes, lipoxins). The most potent chemotactic

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Parapneumonic effusions occur frequently in bacterial pneumonia as a result of **exudative** fluid accumulation within the pleural space. Infections and other forms of inflammatory tissue injury cause increased vascular permeability, leading to the formation of protein-rich exudates that contain a variety of biologically active substances. Under the influence of inflammatory stimuli, cell membrane phospholipids release arachidonic acid, a precursor to the eicosanoid inflammatory mediators (eg, prostanoids, leukotrienes, lipoxins). The most potent chemotactic eicosanoid is **leukotriene B_4**. In contrast, the cysteinyl-containing leukotrienes (eg, LTC_4, LTD_4, LTE_4) cause bronchospasm and increase bronchial mucus secretion and are important in asthma pathogenesis.

(Choice A) Bradykinin is a component of the kinin system. It causes vasodilation, increases vascular permeability, stimulates smooth muscle contraction, and helps mediate pain.

(Choice B) Complement components C3a, C4a, and C5a are inflammatory anaphylotoxins that trigger histamine release from mast cells, resulting in vasodilation and enhanced vascular permeability. C5a also recruits and activates neutrophils, monocytes, eosinophils, and basophils. C4a is the least active of these complement components and plays a minor role in leukocyte recruitment.

(Choice C) Interferon gamma (IFN-γ) activates macrophages, increases MHC expression, and promotes T_H1 cell differentiation. It is produced primarily by activated T cells and natural killer cells.

(Choice D) IL-4 is a cytokine produced by T_H2 cells that activates B cells, induces IgE isotype switching, and promotes T_H2 cell differentiation.

(Choice F) Thromboxane A_2 is an eicosanoid synthesized by platelets that causes vasoconstriction and platelet aggregation.

Educational objective:
Leukotriene B_4 stimulates neutrophil migration to sites of inflammation. Other important chemotactic agents include 5-HETE (leukotriene precursor), complement component C5a, and IL-8.

Immunology	General Principles	Inflammation
Subject	System	Topic

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A 6-month-old boy is brought to the clinic by his mother and grandmother for a routine well-child visit. The child was born full-term and has no medical problems. He recently learned to sit with support and is starting to eat pureed foods. Vital signs and physical examination are normal. As part of the routine pediatric immunization schedule, the pneumococcal conjugate vaccine is ordered. The patient's grandmother says that she recently received the pneumococcal polysaccharide vaccine. Which of the following statements is true regarding the difference between the pneumococcal conjugate and polysaccharide vaccines?

- A. The conjugate vaccine causes less local site reactions than the polysaccharide vaccine
- B. The conjugate vaccine induces a more robust immune response through B and T cell activation
- C. The conjugate vaccine is inactivated while the polysaccharide vaccine is live attenuated
- D. The conjugate vaccine protects against meningitis but the polysaccharide vaccine does not
- E. The conjugate vaccine protects against more pneumococcal strains than the polysaccharide vaccine

Submit

A 6-month-old boy is brought to the clinic by his mother and grandmother for a routine well-child visit. The child was born full-term and has no medical problems. He recently learned to sit with support and is starting to eat pureed foods. Vital signs and physical examination are normal. As part of the routine pediatric immunization schedule, the pneumococcal conjugate vaccine is ordered. The patient's grandmother says that she recently received the pneumococcal polysaccharide vaccine. Which of the following statements is true regarding the difference between the pneumococcal conjugate and polysaccharide vaccines?

- A. The conjugate vaccine causes less local site reactions than the polysaccharide vaccine (1%)
- ✓ B. The conjugate vaccine induces a more robust immune response through B and T cell activation (79%)
- C. The conjugate vaccine is inactivated while the polysaccharide vaccine is live attenuated (7%)
- D. The conjugate vaccine protects against meningitis but the polysaccharide vaccine does not (2%)
- E. The conjugate vaccine protects against more pneumococcal strains than the polysaccharide vaccine (7%)

Omitted
Correct answer
B

79%
Answered correctly

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Time Spent

02/24/2020
Last Updated

Explanation

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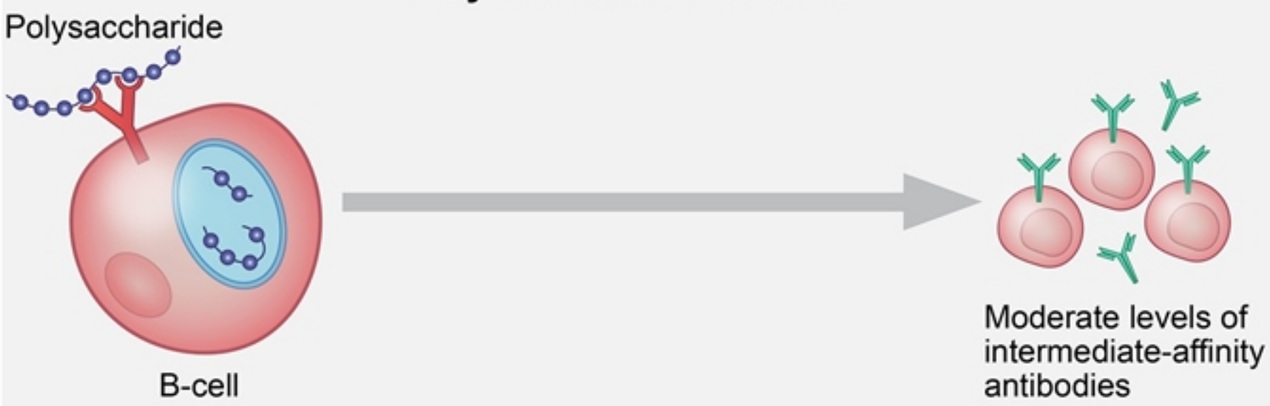
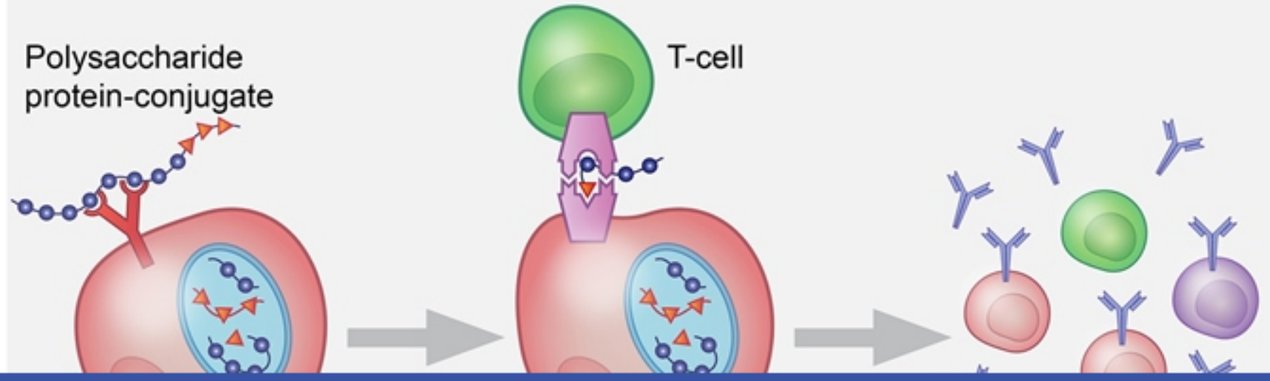
Polysaccharide vaccine



Advantages

- ↓ Incidence of replacement strains due to lack of mucosal immunity

Conjugate vaccine



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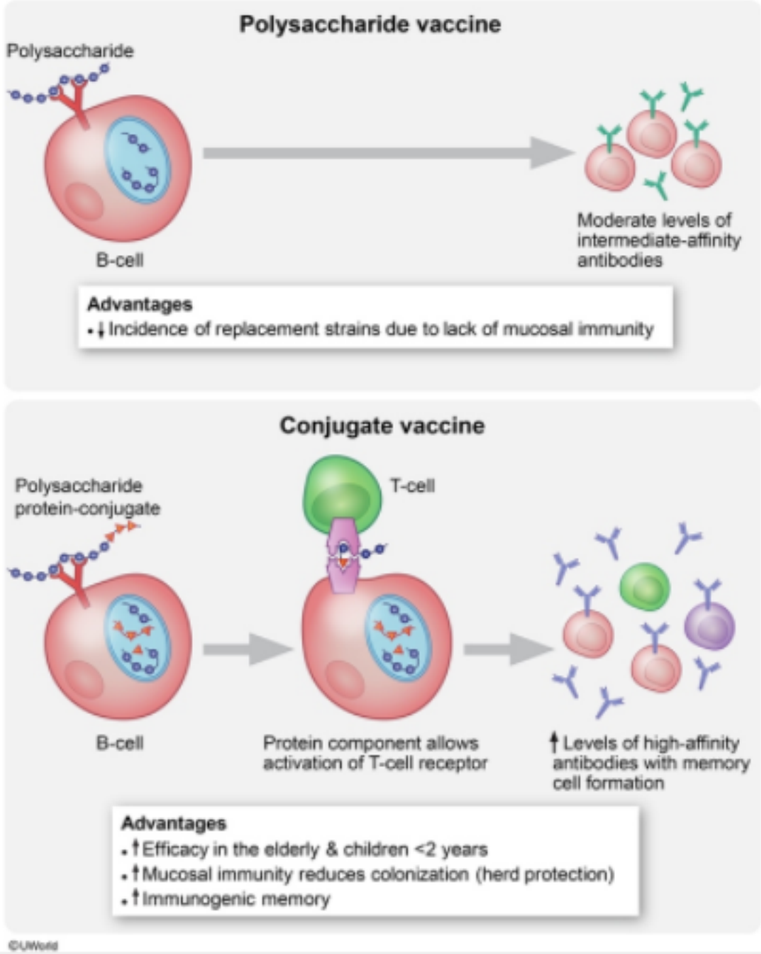

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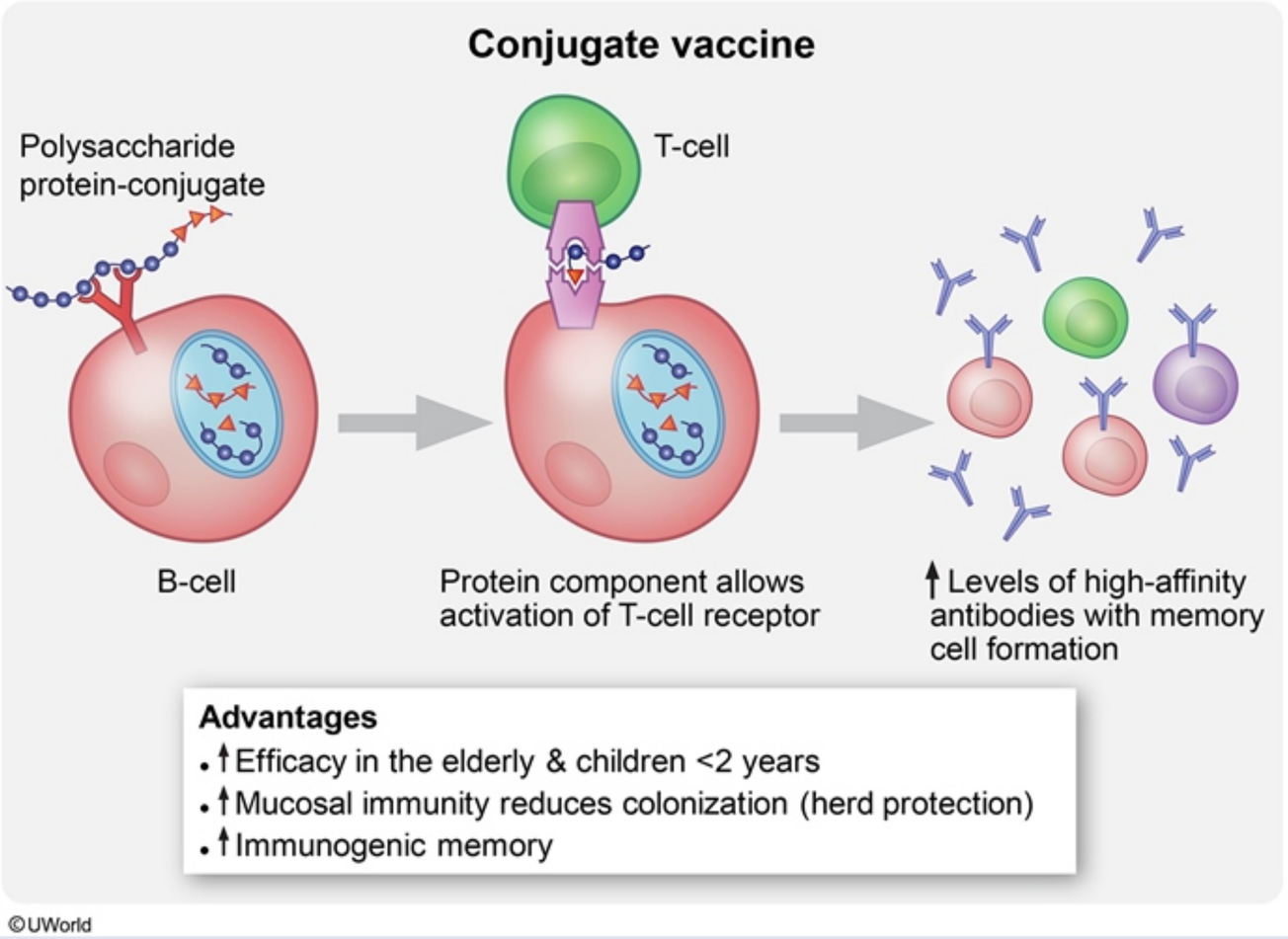

Streptococcus pneumoniae is a common cause of invasive infection (eg, meningitis, sepsis) in children, particularly those age <2. Routine childhood immunization has dramatically reduced the incidence of *S pneumoniae* infection in infancy. Pneumococcal strains are identified by the polysaccharide components of their capsule. These polysaccharides are included in vaccines to provide strain-specific immunity.

The 2 types of pneumococcal vaccines are the polysaccharide and conjugate vaccines. The 23-valent pneumococcal **polysaccharide vaccine**

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The 2 types of pneumococcal vaccines are the polysaccharide and conjugate vaccines. The 23-valent pneumococcal **polysaccharide vaccine** (PPSV23, Pneumovax) protects against a wider range of serotypes **(Choice E)**, but antibody levels decline over approximately 5 years. In addition, PPSV23 is **not immunogenic** in children **age <2** due to their relatively immature humoral antibody response. Therefore, PPSV23 is recommended for all adults age >65 and for those age 2-64 with certain medical conditions (eg, diabetes, chronic pulmonary or cardiovascular disease).

The 13-valent pneumococcal **conjugate vaccine** (PCV13, Prevnar) contains a nontoxic diphtheria protein conjugated to the polysaccharides that boosts the immune response through **T cell recruitment**. This conjugation allows for development of memory B cells, higher and longer-lasting antibody levels, and less mucosal carriage (herd immunity). Therefore, PCV13 is **strongly immunogenic** in infancy and part of routine childhood vaccinations. Similar to PPSV23, PCV13 is recommended for immunocompromised patients and adults age >65.

(Choice A) The rate of local site reactions is similar between PCV13 and PPSV23, approximately 40%-50%. Most local site reactions are minor (eg, transient pain, redness, swelling).

(Choice C) PPSV23 is a polysaccharide capsular subunit, not a live attenuated vaccine. Examples of live attenuated vaccines include the rotavirus, varicella, and measles-mumps-rubella vaccinations.

(Choice D) Both PPSV23 and PCV13 provide strain-specific protection against invasive disease, including meningitis and sepsis.

Educational objective:
Pneumococcal conjugate vaccines are strongly immunogenic in infancy due to both B and T cell recruitment. They provide higher, longer-lasting antibody titers relative to pneumococcal polysaccharide vaccines. The pneumococcal polysaccharide vaccine is poorly immunogenic in infants due to their relatively immature humoral antibody response.

References

- Impact of conjugate pneumococcal vaccines on the changing epidemiology of pneumococcal infections

The 13-valent pneumococcal **conjugate vaccine** (PCV13, Prevnar) contains a nontoxic diphtheria protein conjugated to the polysaccharides that boosts the immune response through **T cell recruitment**. This conjugation allows for development of memory B cells, higher and longer-lasting antibody levels, and less mucosal carriage (herd immunity). Therefore, PCV13 is **strongly immunogenic** in infancy and part of routine childhood vaccinations. Similar to PPSV23, PCV13 is recommended for immunocompromised patients and adults age >65.

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Pneumococcal conjugate vaccines are strongly immunogenic in infancy due to both B and T cell recruitment. They provide higher, longer-lasting antibody titers relative to pneumococcal polysaccharide vaccines. The pneumococcal polysaccharide vaccine is poorly immunogenic in infants due to their relatively immature humoral antibody response.

References

- Impact of conjugate pneumococcal vaccines on the changing epidemiology of pneumococcal infections
- A review of the evidence to inform pneumococcal vaccine recommendations for risk groups aged 2 years and older
- Optimising the use of conjugate vaccines to prevent disease caused by Haemophilus influenzae type b, Neisseria meningitidis and Streptococcus pneumoniae.

Immunology	Allergy & Immunology	Immunizations
Subject	System	Topic

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A 6-year-old boy is evaluated for recurrent infections and failure to thrive. He has been hospitalized for pneumococcal pneumonia twice and has had 5 episodes of otitis media, requiring placement of tympanostomy tubes. The patient also has a history of prolonged diarrhea caused by *Cryptosporidium parvum*. Physical examination shows large tonsils, palpable lymph nodes, and hepatosplenomegaly. Further evaluation shows that the patient has defective signaling between activated CD4+ T cells and B lymphocytes. Which of the following immunoglobulins likely has the highest serum concentration in this patient?

- A. IgA
- B. IgD
- C. IgE
- D. IgG
- E. IgM

Submit

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- A. IgA (5%)
- B. IgD (1%)
- C. IgE (3%)
- D. IgG (5%)
- ✓ E. IgM (84%)

Omitted
Correct answer
E

84%
Answered correctly

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Last Updated

Explanation

Hyperimmunoglobulin M syndrome	
Etiology	• Deficient CD40L-CD40 interaction

Explanation

Hyperimmunoglobulin M syndrome	
Etiology	• Deficient CD40L-CD40 interaction • Failure of antibody class switching in B cells
Inheritance	• X-linked recessive (CD40L deficiency)
Clinical features	• Recurrent sinopulmonary & gastrointestinal infection • Infections with opportunistic pathogens • Failure to thrive
Diagnosis	• ↑ IgM • ↓↓ IgG, IgA, IgE • Flow cytometry shows absent CD40L on CD4+ T cells

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This patient's recurrent sinopulmonary and gastrointestinal infections, failure to thrive, and evidence of defective signaling between CD4+ T cells and B cells is consistent with **hyperimmunoglobulin M** (hyper-IgM) **syndrome**. Hyper-IgM syndrome results from a defect in **class switching** in B lymphocytes. Class switching allows B cells to modify production of immunoglobulins from one isotype to another (eg, from IgM to IgA). This occurs by splicing out DNA coding for different types of the **heavy chain constant region** until the desired isotype is reached. The **variable region,** and therefore the antigenic specificity of the antibody, stays the same.

Normally, class switching occurs when an activated CD4+ T cell uses its **CD40 ligand** (CD40L) to bind to CD40 on the B cell surface. Either CD40L deficiency (most common, X-linked recessive) or CD40 deficiency (rare, autosomal recessive) will prevent normal class switching. As a result, B cells remain in their native IgM-producing state. Serum IgM levels are usually **high** whereas IgG, IgA, and IgE are markedly **low** or

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Educational objective:

Hyperimmunoglobulin M (hyper-IgM) syndrome results from defective immunoglobulin class switching due to a defect in CD40 ligand-CD40 interaction. Absence of the CD40 ligand is the most common cause and is inherited in an X-linked recessive pattern. Clinical features include recurrent sinopulmonary, gastrointestinal, and opportunistic infections.

References

- The hyper-IgM syndromes.

Immunology	Allergy & Immunology	Hyper-igm syndrome
Subject	System	Topic

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An 8-year-old male is brought to his pediatrician's office by his mother. The child has had a runny nose, sore throat, cough, and low-grade fever for the past 24 hours. The patient's mother recalls that several of the child's friends have been ill recently with similar symptoms. The mother asks whether the child will need antibiotics for his condition. His pediatrician recommends symptomatic therapy and feels that his illness is most likely of viral etiology. Cytotoxic CD8+ lymphocytes are able to kill virus-infected nasal epithelial cells once sensitized. Cytotoxic CD8+ lymphocyte receptors recognize foreign proteins on the epithelial cell surface. Foreign proteins are presented on the epithelial cell surface by MHC molecules. These MHC molecules comprise which of the following components?

A. MHC class I heavy chain only

B. MHC class I heavy chain and β_2-microglobulin

C. MHC class I heavy chain and IgG

D. MHC class II alpha-chain and beta-chain

E. MHC class II alpha-chain only

Submit

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- A. MHC class I heavy chain only (17%)
- ✓ B. MHC class I heavy chain and β_2-microglobulin (65%)
- C. MHC class I heavy chain and IgG (7%)
- D. MHC class II alpha-chain and beta-chain (6%)
- E. MHC class II alpha-chain only (2%)

Omitted
Correct answer
B

65%
Answered correctly

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Explanation

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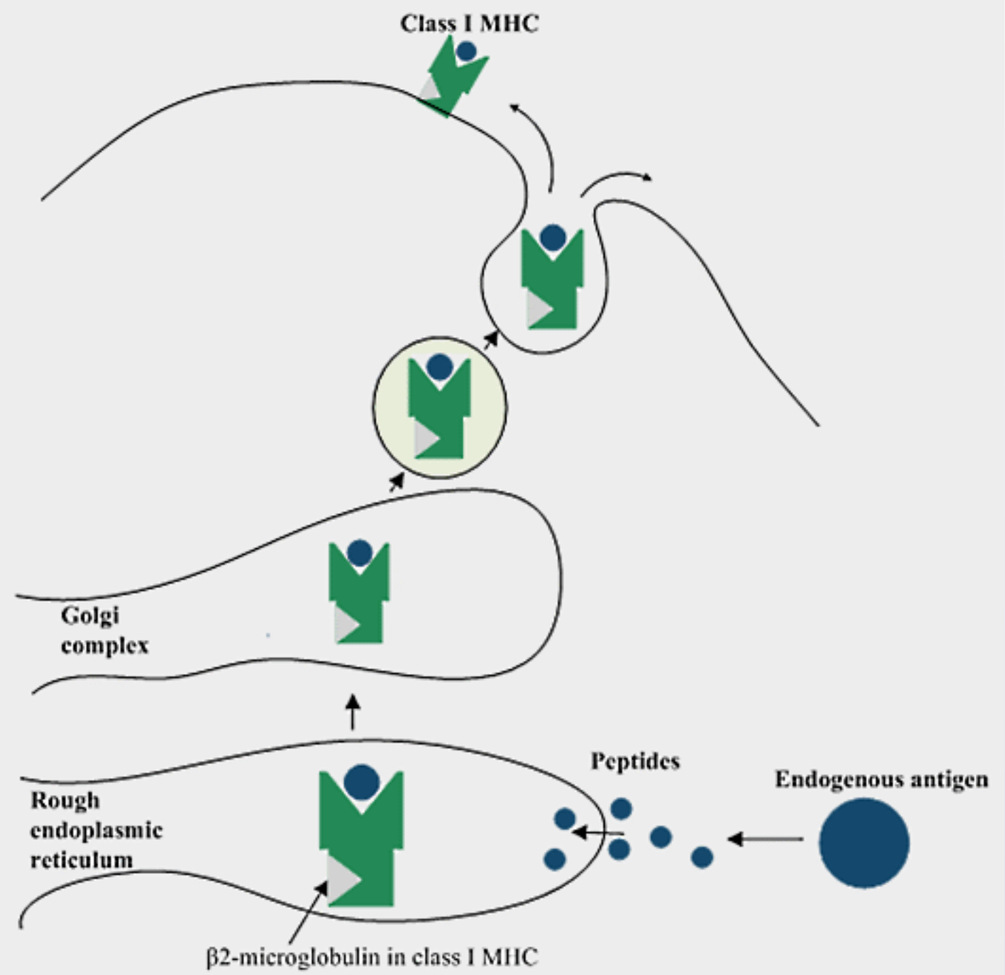

Antigens are presented to cytotoxic CD8+ T-lymphocytes in association with MHC class I molecules. MHC class I is present on the surface of all nucleated cells. Each molecule of MHC class I protein consists of a single heavy chain and an associated β_2-microglobulin. Heavy chains are highly polymorphic, allowing them to present a large variety of antigens.

Antigens are presented to cytotoxic CD8⁺ T-lymphocytes in association with MHC class I molecules. MHC class I is present on the surface of all nucleated cells. Each molecule of MHC class I protein consists of a single heavy chain and an associated β_2-microglobulin. Heavy chains are highly polymorphic, allowing them to present a large variety of antigens.

After penetrating a cell, the virus uncoats and releases its core proteins. Some viral polypeptides are processed in the host cell cytoplasm and combined with MHC class I in the endoplasmic reticulum. The foreign antigen is then presented in association with MHC class I protein on the surface of the infected cell, signaling to CD8⁺ lymphocytes that the cell needs to be destroyed. The infected cell is ultimately eliminated via apoptosis.

Important features of MHC class I and II molecules are compared below:

Features	MHC class I	MHC class II
Structure	Heavy chain and β2-microglobulin	Alpha and beta polypeptide chains
Location	All nucleated cells	Antigen-presenting cells (B-cells, macrophages, dendritic cells, Langerhans cells)
Function	Present antigen to CD8+ cytotoxic T-cells	Present antigen to CD4+ T-helper lymphocytes
Type of antigen	Viruses, tumor proteins; antigens are processed in the cytoplasm	Bacterial; antigens are phagocytosed and digested by lysosomes within which antigen binds to MHC II
Antigen presentation results in:	Apoptosis of the presenting cell	Activation of TH cells, which stimulate the humoral and cell-mediated immune responses

apoptosis.

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Antigen presentation results in:	Apoptosis of the presenting cell	Activation of TH cells, which stimulate the humoral and cell-mediated immune responses

(Choice D) MHC class II molecules consist of two polypeptide chains, alpha and beta. MHC class II molecules are present on the surface of antigen-presenting cells, including B-lymphocytes, macrophages, dendritic cells of the viscera, and Langerhans cells of the skin. Foreign antigens taken up by phagocytosis are degraded in lysosomes and presented to $CD4^+$ T-helper cells in association with MHC II.

Educational objective:

$CD8^+$ cells recognize foreign antigens presented with MHC class I proteins. Each MHC class I molecule consists of a heavy chain and a β_2-microglobulin.

Function	Present antigen to CD8+ cytotoxic T-cells	Present antigen to CD4+ T-helper lymphocytes
Type of antigen	Viruses, tumor proteins; antigens are processed in the cytoplasm	Bacterial; antigens are phagocytosed and digested by lysosomes within which antigen binds to MHC II
Antigen presentation results in:	Apoptosis of the presenting cell	Activation of TH cells, which stimulate the humoral and cell-mediated immune responses

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$CD8^+$ cells recognize foreign antigens presented with MHC class I proteins. Each MHC class I molecule consists of a heavy chain and a β_2-microglobulin.

References

- Intracellular assembly and trafficking of MHC class I molecules.
- MHC class I assembly: out and about.

Immunology	General Principles	Immunology principles
Subject	System	Topic

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A 57-year-old woman with autosomal dominant polycystic kidney disease develops end-stage renal disease and undergoes deceased-donor kidney transplantation. During the operation, the surgeon notices that the graft becomes cyanotic and mottled soon after its blood vessels are connected with those of the recipient. Blood flow to the graft ceases, and no urine is produced. Which of the following best explains the findings observed by the surgeon?

A. Activation of recipient T lymphocytes

B. Antibody recognition of graft HLA components

C. Degranulation of recipient mast cells and basophils

D. Donor T lymphocyte–mediated vasculopathy

E. Severe renal graft atherosclerosis

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- A. Activation of recipient T lymphocytes (11%)
- ✓ B. Antibody recognition of graft HLA components (69%)
- C. Degranulation of recipient mast cells and basophils (8%)
- D. Donor T lymphocyte–mediated vasculopathy (7%)
- E. Severe renal graft atherosclerosis (3%)

Omitted
Correct answer
B

69%
Answered correctly

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03/04/2020
Last Updated

Explanation

Transplant rejection reactions			
Type of rejection	Onset time	Etiology	Morphology
			• Gross mottling & cyanosis

Transplant rejection reactions			
Type of rejection	**Onset time**	**Etiology**	**Morphology**
Hyperacute	Minutes to hours	• Preformed recipient antibodies against graft antigens	• Gross mottling & cyanosis • Arterial fibrinoid necrosis & capillary thrombotic occlusion
Acute	Usually <6 months	• Exposure to donor antigens induces activation of naive immune cells • Predominantly **cell-mediated**	• **Cellular:** lymphocytic interstitial infiltrate & endotheliitis • Humoral: C4d deposition, neutrophilic infiltrate, necrotizing vasculitis
Chronic	Months to years	• Chronic low-grade immune response refractory to immunosuppression • Predominantly **humoral**	• Vascular wall thickening & luminal narrowing • Interstitial fibrosis & parenchymal atrophy

This patient is experiencing **hyperacute rejection** of a renal transplant. Hyperacute rejection is an **antibody-mediated reaction** (ie, type II hypersensitivity) caused by **preformed IgG antibodies** in the recipient that are directed against donor antigens. These are commonly anti-HLA antibodies (eg, formed during prior blood transfusion or pregnancy) or ABO blood group antibodies.

Hyperacute rejection is usually diagnosed in the operating room when the kidney becomes **cyanotic and mottled** after anastomosis of the donor and recipient blood vessels. Perfusion through the transplanted organ ceases immediately due to antibody- and complement-mediated **vascular injury** with subsequent **thrombotic occlusion**. This rapidly leads to ischemic necrosis of the glomeruli and renal cortex with little to **no urine output** and irreversible **graft loss**.

To minimize the risk of hyperacute rejection, donor and recipient ABO and HLA cross-matching is performed prior to renal transplantation.

(Choice A) Activation of recipient T lymphocytes is the primary mechanism of acute organ transplant rejection. Recipient T cells are sensitized

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		• Predominantly **humoral**	

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To minimize the risk of hyperacute rejection, donor and recipient ABO and HLA cross-matching is performed prior to renal transplantation.

(Choice A) Activation of recipient T lymphocytes is the primary mechanism of acute organ transplant rejection. Recipient T cells are sensitized by donor graft antigens, leading to cell-mediated (ie, type IV hypersensitivity) rejection that typically occurs within 6 months after transplant. This type of rejection is generally reversible with increased doses of immunosuppression.

(Choice C) Degranulation of mast cells and basophils occurs during a type I hypersensitivity reaction (eg, allergic response), which is not involved in organ transplant rejection.

(Choice D) Graft versus host disease results from donor T lymphocytes activating against recipient antigens, leading to vasculitis and tissue damage of recipient organs (eg, skin, liver, gastrointestinal tract).

(Choice E) Atherosclerotic stenosis of the transplanted renal artery can occur over time, but it would not cause acute graft ischemia with cyanosis and mottling at the time of transplant surgery.

Educational objective:
Hyperacute rejection is caused by preformed antibodies in the recipient that recognize and attack donor antigens (ie, type II hypersensitivity). These are often anti-ABO blood group or anti-HLA antibodies. Vascular injury and capillary thrombotic occlusion lead to rapid ischemic necrosis of the renal graft, often evidenced by gross cyanosis and mottling immediately following graft perfusion.

References

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References

- Root cause analysis of limitations of virtual crossmatch for kidney allocation to highly-sensitized patients.
- The major histocompatibility complex in transplantation.

Immunology	Allergy & Immunology	Transplant rejection
Subject	System	Topic

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A 75-year-old man is hospitalized due to respiratory distress. The patient developed fever, cough, and muscle aches 4 days prior to admission. He is otherwise healthy and has no chronic medical conditions. The patient has received all recommended vaccinations, including a yearly flu vaccine. Temperature is 39 C (102.2 F), blood pressure is 110/65 mm Hg, pulse is 115/min, and respirations are 29/min. Chest x-ray shows bilateral infiltrates. Reverse transcriptase PCR of a specimen from a nasopharyngeal swab reveals a strain of influenza A virus that was included in the seasonal trivalent flu vaccine. The patient lives with his 50-year-old son, who received the same vaccine but did not develop the infection. Which of the following factors most likely increased this patient's risk of vaccine failure compared with that of his son?

A. Decreased overall quality of antibodies

B. Decreased production of naive B lymphocytes

C. Diminished levels of memory T lymphocytes

D. Increased apoptosis induced by neutrophils

E. Increased phagocytosis by macrophages

Submit

A 75-year-old man is hospitalized due to respiratory distress. The patient developed fever, cough, and muscle aches 4 days prior to admission. He is otherwise healthy and has no chronic medical conditions. The patient has received all recommended vaccinations, including a yearly flu vaccine. Temperature is 39 C (102.2 F), blood pressure is 110/65 mm Hg, pulse is 115/min, and respirations are 29/min. Chest x-ray shows bilateral infiltrates. Reverse transcriptase PCR of a specimen from a nasopharyngeal swab reveals a strain of influenza A virus that was included in the seasonal trivalent flu vaccine. The patient lives with his 50-year-old son, who received the same vaccine but did not develop the infection. Which of the following factors most likely increased this patient's risk of vaccine failure compared with that of his son?

A. Decreased overall quality of antibodies (15%)

✓ B. Decreased production of naive B lymphocytes (37%)

C. Diminished levels of memory T lymphocytes (45%)

D. Increased apoptosis induced by neutrophils (0%)

E. Increased phagocytosis by macrophages (0%)

Omitted
Correct answer
B

37%
Answered correctly

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Explanation

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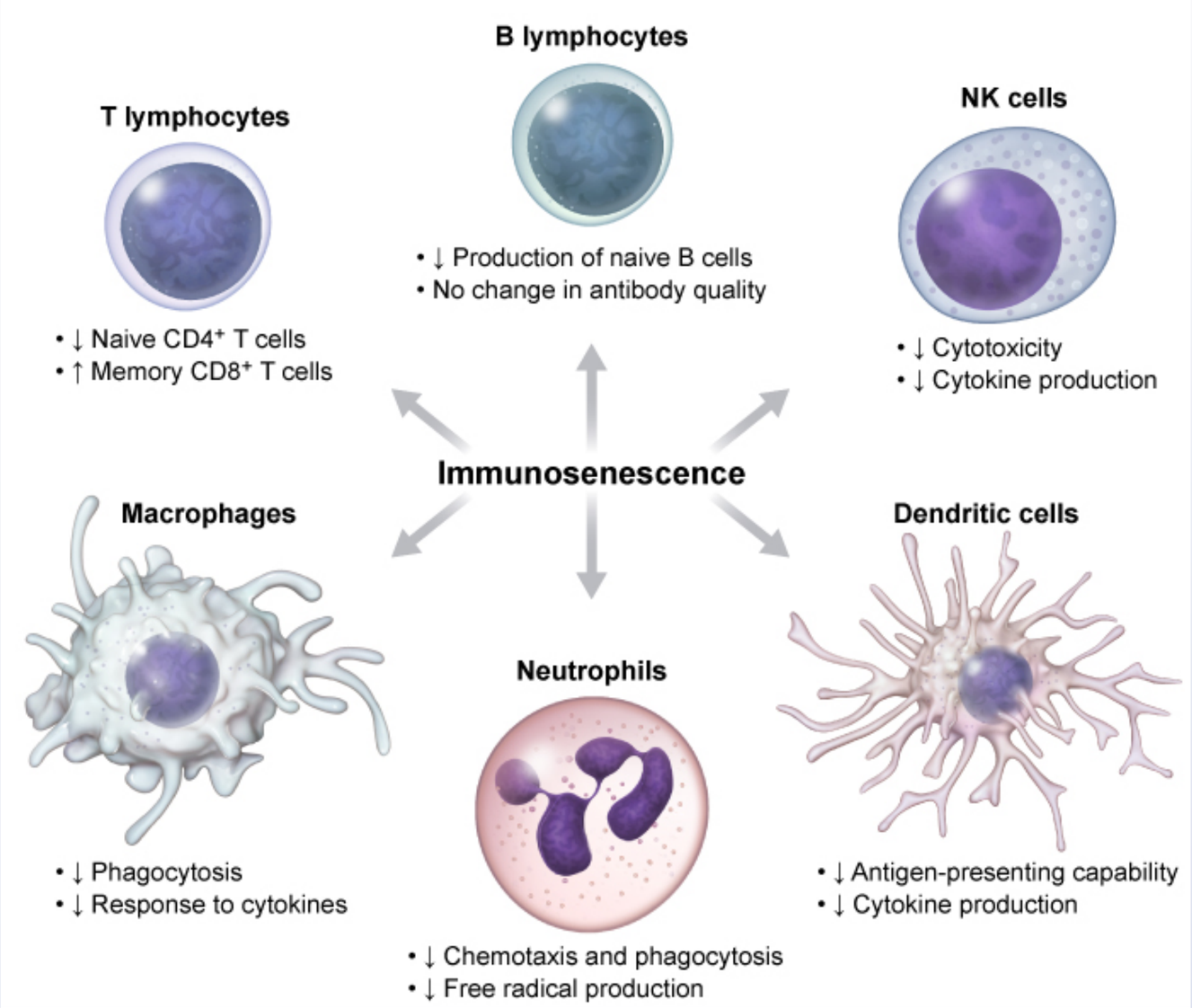

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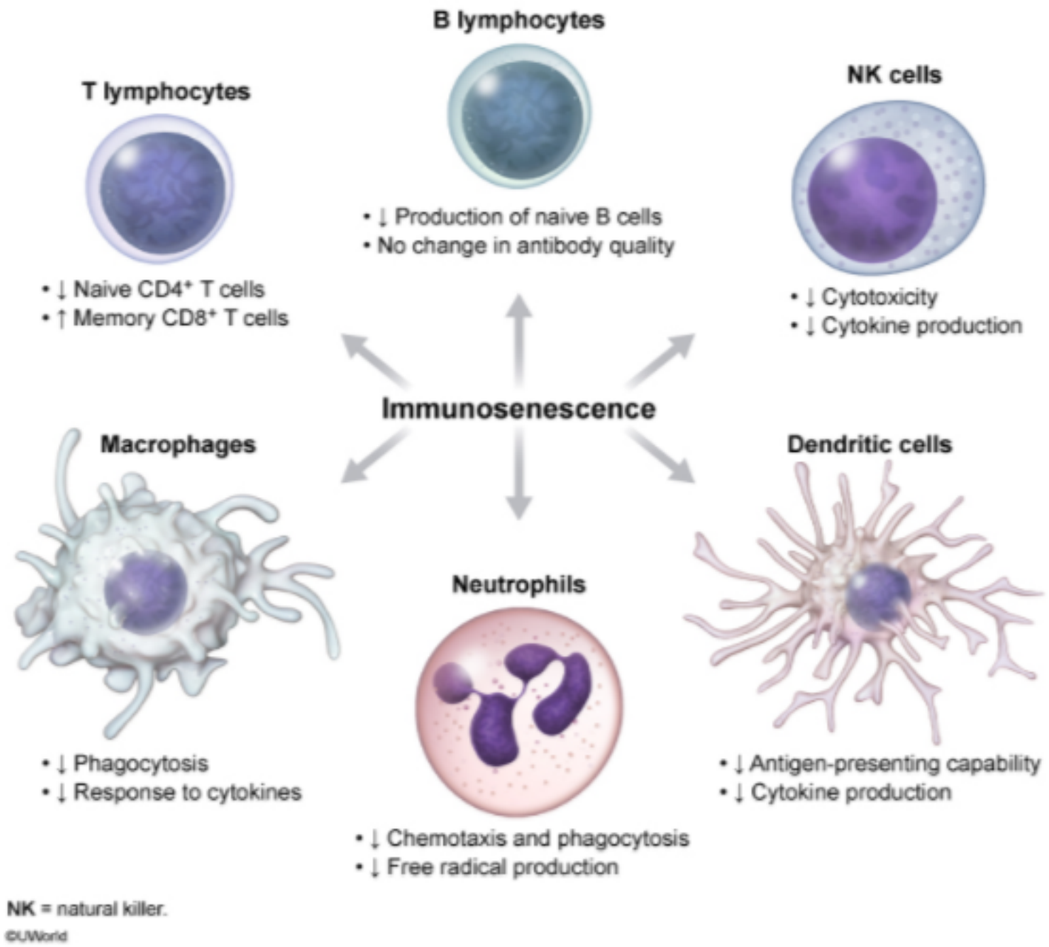

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• ↓ Free radical production

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Most of the protection provided by vaccines depends on antibodies generated by an immune response to pathogen-specific antigens. These antibodies can bind to the pathogen and directly neutralize it or facilitate elimination of the pathogen through phagocytosis, complement fixation, and/or antibody-dependent cytotoxicity. The risk of primary **vaccine failure** is increased in patients with altered immune function, including those with atopic disorders (eg, asthma, eczema), steroid use, or age-related immune decline (eg, **immunosenescence**).

The loss of telomere length during normal aging particularly affects rapidly dividing immune cells (eg, bone marrow stem cells, lymphocyte precursors), resulting in **decreased** production of **naive B and T lymphocytes**. Aging is also associated with chronic low-grade inflammation that causes much of the remaining naive lymphocyte pool to differentiate into memory lymphocytes against previously encountered antigens. These changes **impair** the adaptive immune **response to novel antigens** (eg, pathogens, vaccinations) and predispose these patients to vaccine failure and increased susceptibility to infection.

(Choices A and C) Antibody quality (ie, avidity for the target antigen) and levels of memory B and T lymphocytes are preserved with age, allowing most aging individuals to mount an effective immune response to previously encountered antigens.

(Choice D) Neutrophil-induced apoptosis is reduced in aging individuals, increasing susceptibility for nonhealing wounds/infections. However, a change in neutrophil function would not significantly impact the vaccine response.

(Choice E) Phagocytosis and antigen presentation by dendritic cells and macrophages decline with age, further impairing the immune response to novel antigens.

Educational objective:
Immunosenescense is the normal age-related decline that impairs most aspects of immune function, including the production of naive B and T cells. This results in a diminished antibody-based immune response to novel antigens (eg, infections, vaccinations). The immune response to previously experienced pathogens is typically intact due to normal or increased levels of memory B and T cells and preserved antibody quality.

References

- Aging of the Immune System: How Much Can the Adaptive Immune System Adapt?

Immunology Allergy & Immunology Aging

A 23-year-old man comes to the physician with dysuria and increased urinary frequency. He is an active duty member of the US military and recently returned from sub-Saharan Africa, where he had been stationed for the last year. The patient's symptoms have persisted for several months and have failed to resolve following antibiotic treatment. His blood eosinophil count is elevated. Urine microscopy shows schistosome eggs. He is started on praziquantel and experiences improvement in his symptoms. The elevated eosinophils in this patient contribute to the host defense against schistosomiasis through which of the following mechanisms?

- A. Antibody-dependent cell-mediated cytotoxicity
- B. B lymphocyte chemotaxis
- C. Complement activation
- D. Immediate hypersensitivity
- E. MHC class I antigen processing

Submit

A 23-year-old man comes to the physician with dysuria and increased urinary frequency. He is an active duty member of the US military and recently returned from sub-Saharan Africa, where he had been stationed for the last year. The patient's symptoms have persisted for several months and have failed to resolve following antibiotic treatment. His blood eosinophil count is elevated. Urine microscopy shows schistosome eggs. He is started on praziquantel and experiences improvement in his symptoms. The elevated eosinophils in this patient contribute to the host defense against schistosomiasis through which of the following mechanisms?

- ✓ A. Antibody-dependent cell-mediated cytotoxicity (43%)
- B. B lymphocyte chemotaxis (8%)
- C. Complement activation (11%)
- D. Immediate hypersensitivity (29%)
- E. MHC class I antigen processing (6%)

Omitted
Correct answer
A

43%
Answered correctly

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Last Updated

Explanation

Parasitic killing by eosinophils

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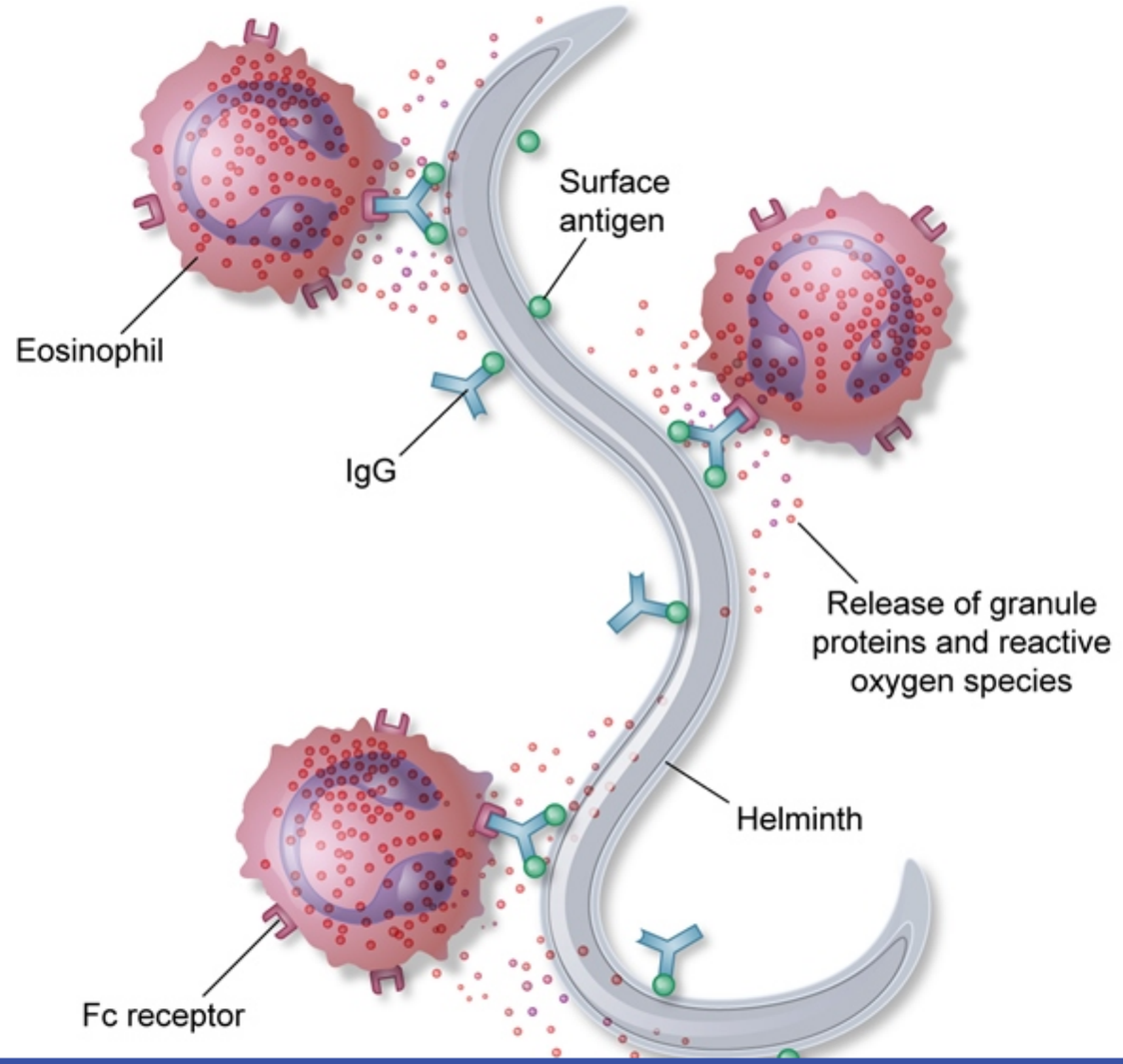
Parasitic killing by eosinophils



Eosinophils perform the following functions:

- **Parasitic defense:** Eosinophil proliferation and activation during multicellular parasitic infection is stimulated by **IL-5** produced by T_H2 and mast cells (not to be confused with IL-4, which stimulates IgE production). When a parasite invades the mucosa or enters the bloodstream, it is coated by IgG and IgA antibodies that bind the Fc receptors located on the eosinophil cell surface. This triggers eosinophil degranulation and release of cytotoxic proteins (eg, **major basic protein**) and reactive oxygen intermediates, substances that damage and destroy antibody-bound parasites. This mechanism is an example of **antibody-dependent cell-mediated cytotoxicity** (ADCC), which is also used by macrophages, neutrophils, and natural killer cells.

- **Type I hypersensitivity reactions:** Eosinophils also synthesize prostaglandins, leukotrienes, and cytokines that contribute to the inflammation seen in **late-phase** type 1 hypersensitivity and chronic allergic reactions.

(Choice B) Eosinophils contain a diverse number of immunomodulatory cytokines that are important for directing the T_H2 immune response; but they do not significantly affect B cell chemotaxis.

(Choice C) Complement activation is an important step in antibody-mediated (type II) and immune complex mediated (type III) hypersensitivity reactions. Complement does not play a prominent role in the destruction of parasites by eosinophils.

(Choice D) Immediate (type I) hypersensitivity reactions are primarily mediated by mast cells and basophils. These cells possess Fc receptor-bound IgE on their membranes. Eosinophils contribute to late-phase type 1 hypersensitivity, but this is an allergic response that would not be protective against schistosomiasis.

(Choice E) Eosinophils can phagocytose parasitic antigens and present them in association with MHC class II molecules to stimulate helper T lymphocytes. In contrast, MHC class I antigen processing is involved in inducing a cytotoxic T lymphocyte response against intracellular pathogens (eg, viruses).

Educational objective:
Eosinophils play a role in host defense during multicellular parasitic infection. When stimulated by antibodies bound to a parasitic organism, they destroy the parasite via antibody-dependent cell-mediated cytotoxicity with enzymes from their cytoplasmic granules. Another function of eosinophils is regulation of type I hypersensitivity reactions.

- **Type I hypersensitivity reactions:** Eosinophils also synthesize prostaglandins, leukotrienes, and cytokines that contribute to the inflammation seen in **late-phase** type 1 hypersensitivity and chronic allergic reactions.

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Educational objective:
Eosinophils play a role in host defense during multicellular parasitic infection. When stimulated by antibodies bound to a parasitic organism, they destroy the parasite via antibody-dependent cell-mediated cytotoxicity with enzymes from their cytoplasmic granules. Another function of eosinophils is regulation of type I hypersensitivity reactions.

References

- IgE, mast cells, basophils, and eosinophils.

Immunology	Allergy & Immunology	Cell mediated immunity
Subject	System	Topic

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A 15-year-old male suffers severe cardiomyopathy following an infective myocarditis from Coxsackie virus and is placed on the cardiac transplant list. Two weeks following his cardiac transplantation from a matched donor, he is suffering dyspnea on exertion. Extensive evaluation is undertaken in this patient including cardiac catheterization and endomyocardial biopsy. Which of the following findings is most consistent with acute graft rejection?

A. Concentric coronary atherosclerosis

B. Dense interstitial lymphocytic infiltrate

C. Perivascular infiltrate with abundant eosinophils

D. Patchy necrosis with granulation tissue

E. Scant inflammatory cells and interstitial fibrosis

Submit

A 15-year-old male suffers severe cardiomyopathy following an infective myocarditis from Coxsackie virus and is placed on the cardiac transplant list. Two weeks following his cardiac transplantation from a matched donor, he is suffering dyspnea on exertion. Extensive evaluation is undertaken in this patient including cardiac catheterization and endomyocardial biopsy. Which of the following findings is most consistent with acute graft rejection?

- A. Concentric coronary atherosclerosis (2%)
- ✓ B. Dense interstitial lymphocytic infiltrate (71%)
- C. Perivascular infiltrate with abundant eosinophils (12%)
- D. Patchy necrosis with granulation tissue (8%)
- E. Scant inflammatory cells and interstitial fibrosis (4%)

Omitted
Correct answer
B

71%
Answered correctly

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02/03/2020
Last Updated

Explanation

The patient described in the question stem is experiencing acute rejection of his cardiac transplant. Acute rejection occurs in approximately 2 of every 5 hearts transplanted and in the large majority of cases occurs by the cell-mediated pathway. In rare cases, cardiac rejection is due to anti-donor host antibodies, and cases of humoral rejection are diagnosed by direct immunofluorescence. The clue that indicates that this patient is experiencing acute rejection is the timeframe of symptoms two weeks post-transplant because acute rejection usually occurs one to four weeks following transplant. The histopathology most consistent with acute rejection on endomyocardial biopsy is a dense infiltrate of mononuclear cells

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(Choice A) Concentric coronary atherosclerosis found on angiography does not indicate rejection. In transplanted patients, finding atherosclerosis on angiography indicates that the donor heart had preexisting atherosclerosis prior to the organ being harvested. Acute cessation of blood flow through an organ immediately after anastomosis of recipient vessels to donor vessels is characteristic of hyperacute rejection. It occurs due to preformed antibodies in the recipient that are directed against donor antigens.

(Choice C) Perivascular infiltrate with abundant eosinophils is a histopathologic presentation consistent with hypersensitivity myocarditis. A large percentage of cases of hypersensitivity myocarditis are believed to occur due to initiation of a new drug therapy, against which the body mounts an atopic response.

(Choice D) Patchy necrosis with granulation tissue is indicative of ischemic damage to the donor heart. Ischemia in a donor heart can occur in a variety of situations including ischemia during attempted resuscitation of the donor patient, during transport of the organ from the donor to the recipient, and acutely during initial perfusion of the organ after transplantation. Ischemia can also occur simply due to atherosclerosis in the donor heart causing classic myocardial ischemia.

(Choice E) Scant inflammatory cells and interstitial fibrosis is most characteristic of chronic rejection. Chronic rejection is a process mediated by host T-lymphocytes and B-lymphocytes as well as antibodies and classically occurs months to years following solid organ transplantation.

Educational Objective:

but symptoms consistent with progressive rejection include those found in heart failure resulting from systolic dysfunction such as dyspnea on exertion or paroxysmal nocturnal dyspnea.

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Educational Objective:
Acute cardiac transplant rejection occurs weeks following transplantation and is primarily a cell-mediated process. On histopathologic analysis of an endomyocardial biopsy, a dense mononuclear lymphocytic infiltrate with cardiac myocyte damage will be visualized. Treatment with immunosuppressive drugs is aimed primarily at preventing this form of rejection.

Immunology	Cardiovascular System	Heart transplantation
Subject	System	Topic

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A 23-year-old woman comes to the physician with migratory joint pains involving her hands and knees. Physical examination shows bilateral tenderness in her wrists and proximal interphalangeal joints. There is also a malar skin rash and generalized lymphadenopathy. A urinalysis reveals proteinuria. Further evaluation shows that the patient's lymphocytes contain a mutated and functionally defective Fas gene product. Which of the following immunologic mechanisms is most likely impaired in this patient as a result of this molecular defect?

- A. Activation-induced T lymphocyte death
- B. Affinity maturation of B lymphocytes
- C. Clonal anergy of T lymphocytes
- D. Isotype switching of B lymphocytes
- E. T_H1 and T_H2 lymphocyte differentiation

Submit

A 23-year-old woman comes to the physician with migratory joint pains involving her hands and knees. Physical examination shows bilateral tenderness in her wrists and proximal interphalangeal joints. There is also a malar skin rash and generalized lymphadenopathy. A urinalysis reveals proteinuria. Further evaluation shows that the patient's lymphocytes contain a mutated and functionally defective Fas gene product. Which of the following immunologic mechanisms is most likely impaired in this patient as a result of this molecular defect?

- ✓ A. Activation-induced T lymphocyte death (64%)
- B. Affinity maturation of B lymphocytes (7%)
- C. Clonal anergy of T lymphocytes (15%)
- D. Isotype switching of B lymphocytes (8%)
- E. T_H1 and T_H2 lymphocyte differentiation (4%)

Omitted
Correct answer
A

64%
Answered correctly

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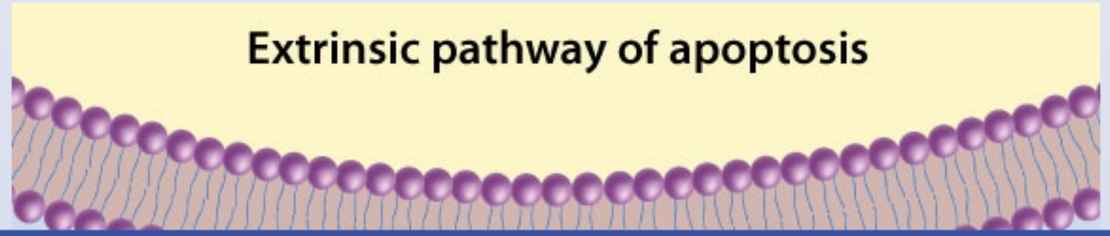
02/20/2020
Last Updated

Explanation



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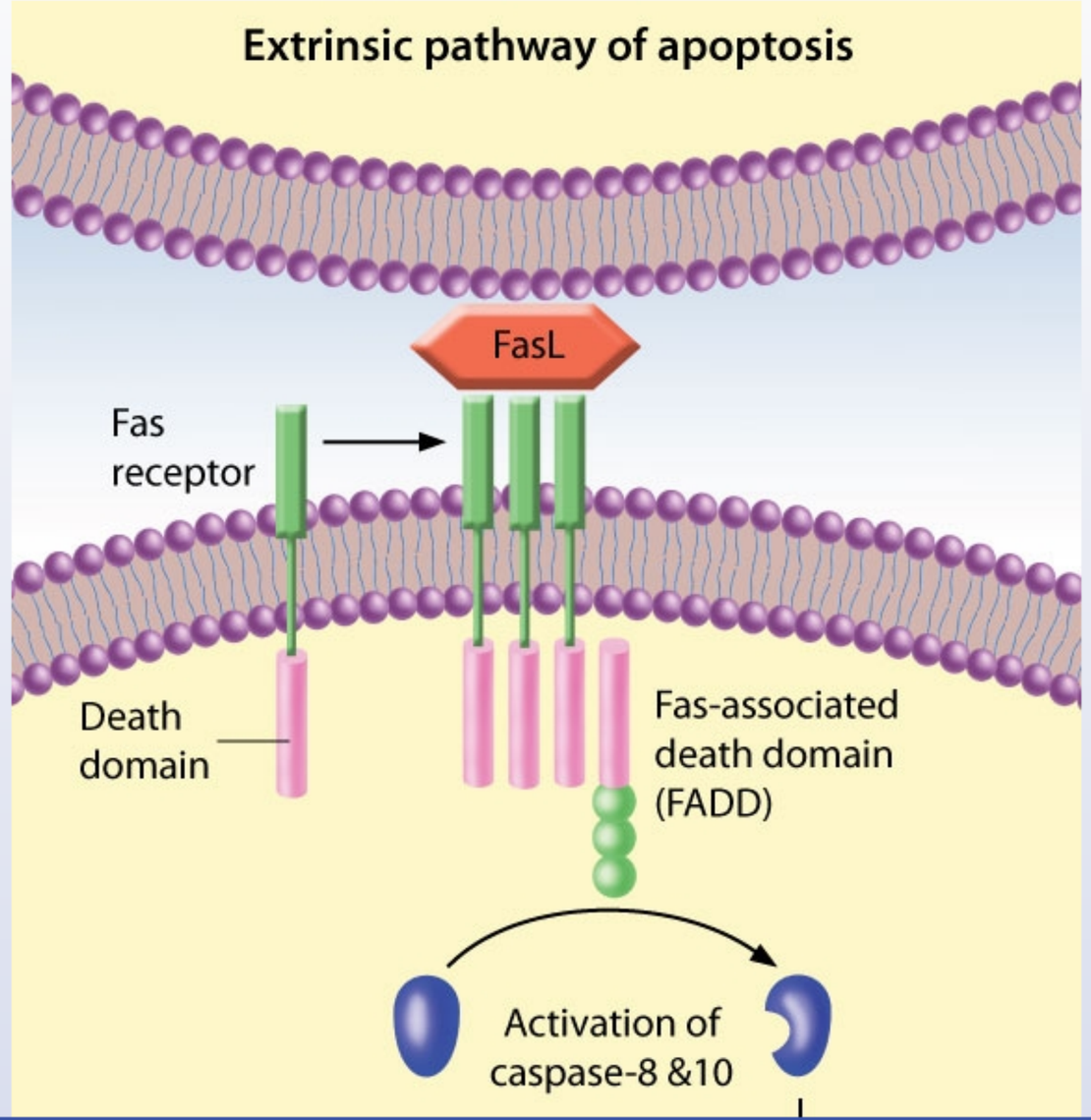

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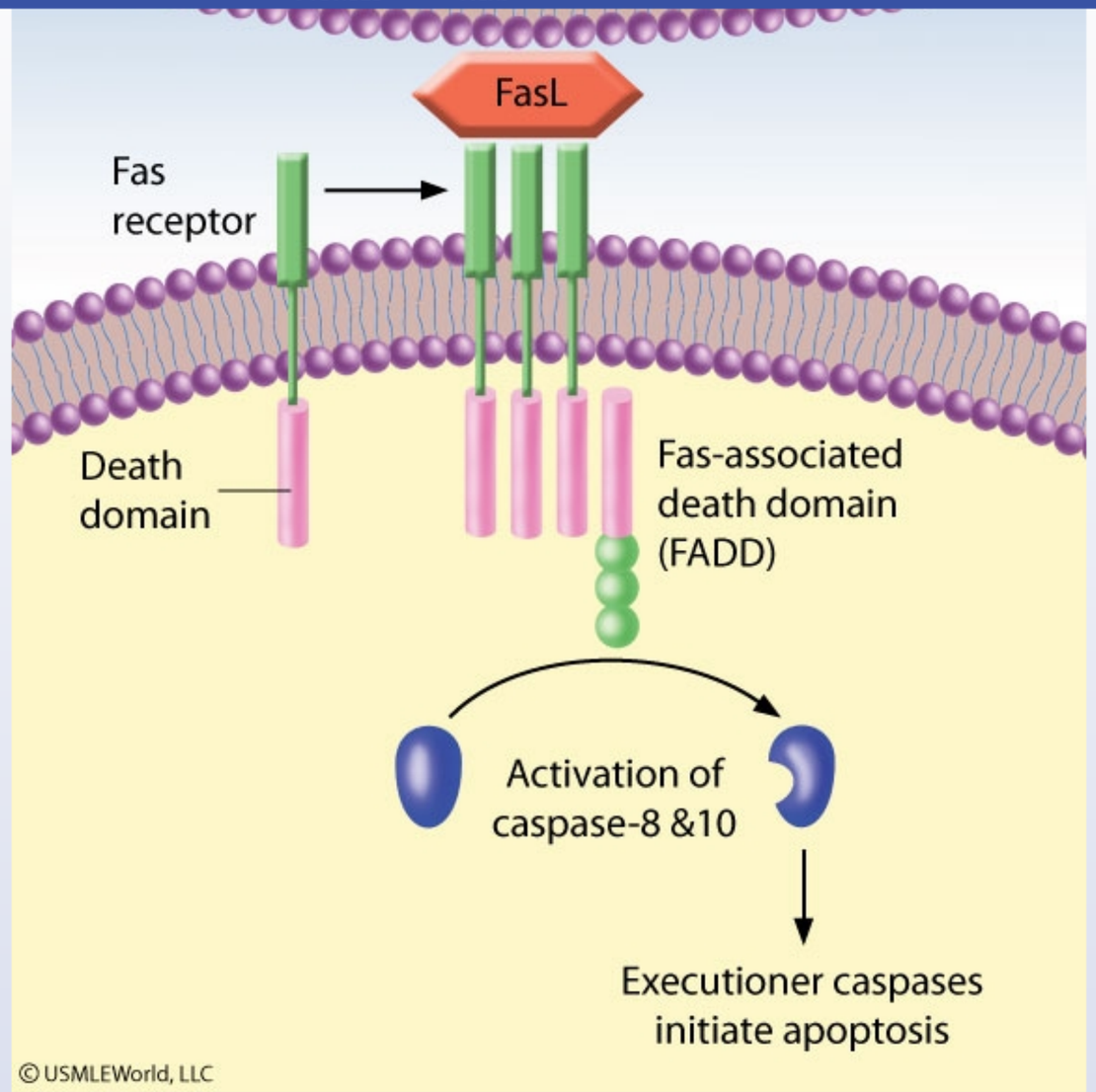

Apoptosis can be triggered by a number of mechanisms, including deprivation of growth factors, DNA damage, intracellular accumulation of

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Apoptosis can be triggered by a number of mechanisms, including deprivation of growth factors, DNA damage, intracellular accumulation of misfolded proteins, mediation by cytotoxic T lymphocytes, and activation of receptors in the TNF receptor family (such as Fas). Fas receptors initiate the extrinsic pathway of apoptosis through a cytoplasmic component known as the death domain. Upon binding Fas ligand (FasL), the receptors trimerize, allowing their death domains to form a binding site for an adapter protein called Fas-associated death domain (FADD). Receptor-bound FADD then stimulates the activation of initiator caspases (8 & 10) that begin an activation cascade culminating in the activation of executioner caspases (3 & 6). These initiate the terminal processes of apoptosis, including cleavage of DNA, fragmentation of the nucleus, organelle autodigestion, and plasma membrane blebbing.

The Fas receptor is expressed on T-lymphocytes and plays an important role in the pathogenesis of numerous diseases, including cancer and autoimmune disorders. Once activated, T lymphocytes begin to express FasL, which can bind to Fas on the same cell or adjacent lymphocytes. During initial clonal expansion, activated T lymphocytes are resistant to Fas-induced apoptosis. However, they become more sensitive with progressive stimulation. In the constant presence of stimulating self-antigens, activated T lymphocytes eventually undergo apoptosis in a process known as activation-induced cell death. Mutations involving Fas or FasL impair this process, resulting in excessive accumulation of autoreactive T-cells and the development of autoimmune diseases such as systemic lupus erythematosus (which this patient appears to have).

(Choice B) As B lymphocytes undergo affinity maturation, cells that exhibit a stronger affinity for the antigen (which acts as a limited growth resource) are able to proliferate more than cells with lower affinity. This results in cells that are more efficient and accurate in binding to pathogens. Affinity maturation does not involve the Fas pathway.

(Choice C) Anergy is a state of prolonged unresponsiveness that occurs in T lymphocytes as a form of immune tolerance. It occurs when self-reactive T cells bind MHC molecules without receiving the necessary costimulatory signal (ie, binding of CD28 on T cells with the B7 on antigen-presenting cells).

(Choice D) Isotype switching is the process through which activated B lymphocytes switch production from IgM immunoglobulins to IgG and IgA isotypes. This process requires the interaction of CD40 on activated B cells with CD40 ligand expressed by activated T cells and is modulated by cytokines secreted by T cells.

(Choice E) On exposure to an antigen, naïve T helper (T_H0) cells differentiate into T_H1 (cell-mediating) and T_H2 (antibody-mediating) subtypes based on the local cytokine milieu. IFN-γ and IL-12 induce T_H1 formation; IL-4 stimulates T_H2 development.

organelle autodigestion, and plasma membrane blebbing.

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Educational objective:
The Fas receptor acts to initiate the extrinsic pathway of apoptosis. Mutations involving the Fas receptor or Fas ligand can prevent apoptosis of autoreactive lymphocytes, thereby increasing the risk of autoimmune disorders such as systemic lupus erythematosus.

References

- Activation-induced cell death in T cells.

A research scientist is comparing surface antigens X and Y that come from 2 different viruses. He obtains antibodies against antigen X from an animal previously exposed to the virus expressing this antigen. These antibodies are then attached to assay plates. Next, a fixed quantity of radiolabeled X antigen is added to the plates. Unlabeled Y antigens are then added in increasing concentrations to each plate, and the plates are washed to remove unbound antigens. Radioactivity is plotted as a function of Y antigen concentration, as shown in the graph below.

Which of the following best describes the results of this experiment?

A. Antigen X and antigen Y have no epitopes in common

B. Antigen X and antigen Y have the same epitopes

C. Antigen Y shares most of the epitopes of antigen X

D. Antigen Y shares some of the epitopes of antigen X

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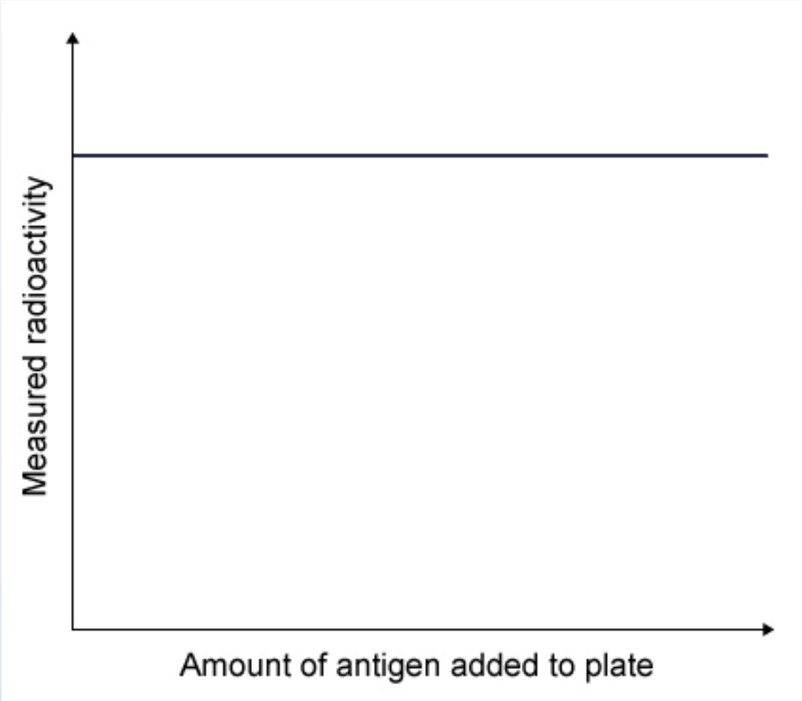

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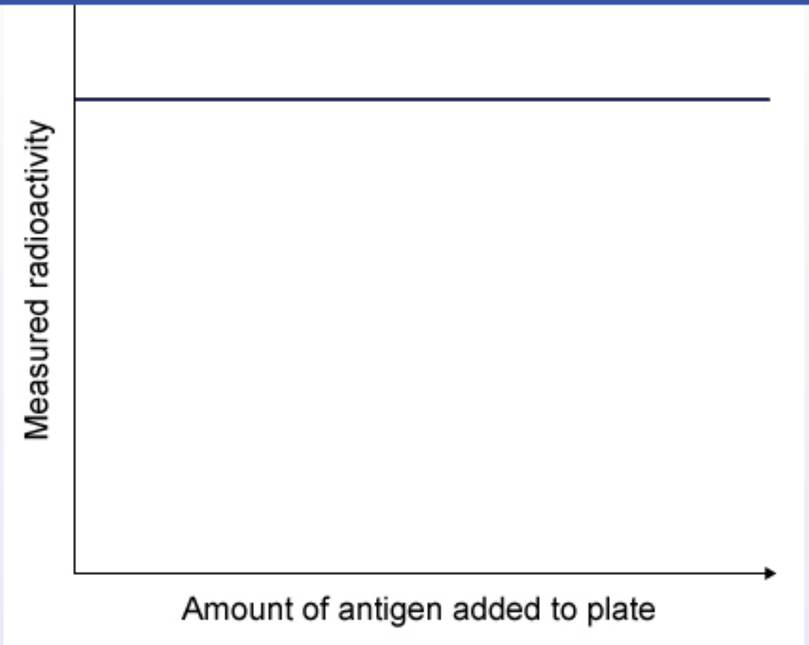

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A. Antigen X and antigen Y have no epitopes in common

B. Antigen X and antigen Y have the same epitopes

C. Antigen Y shares most of the epitopes of antigen X

D. Antigen Y shares some of the epitopes of antigen X

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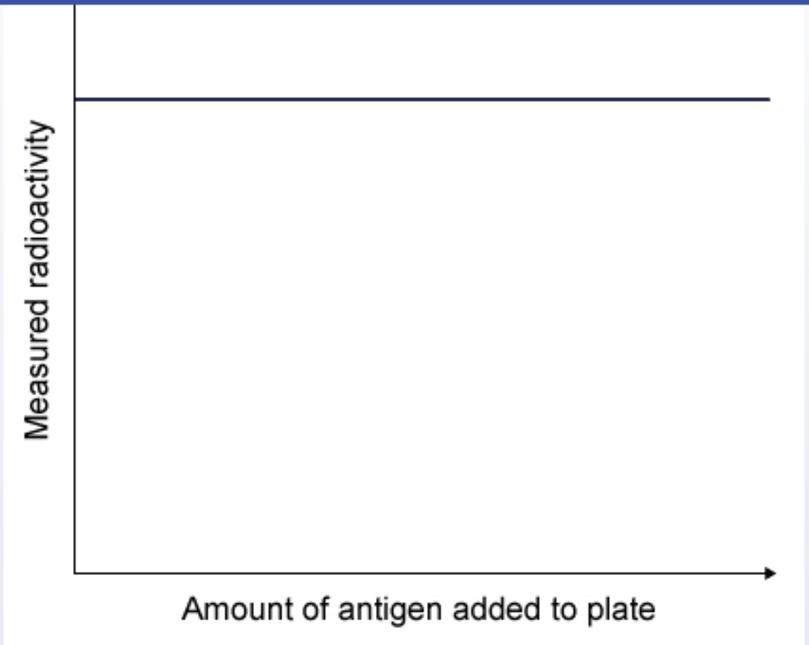

Which of the following best describes the results of this experiment?

- A. Antigen X and antigen Y have no epitopes in common (55%)
- B. Antigen X and antigen Y have the same epitopes (32%)
- C. Antigen Y shares most of the epitopes of antigen X (8%)
- D. Antigen Y shares some of the epitopes of antigen X (3%)

Omitted
Correct answer

55%
Answered correctly

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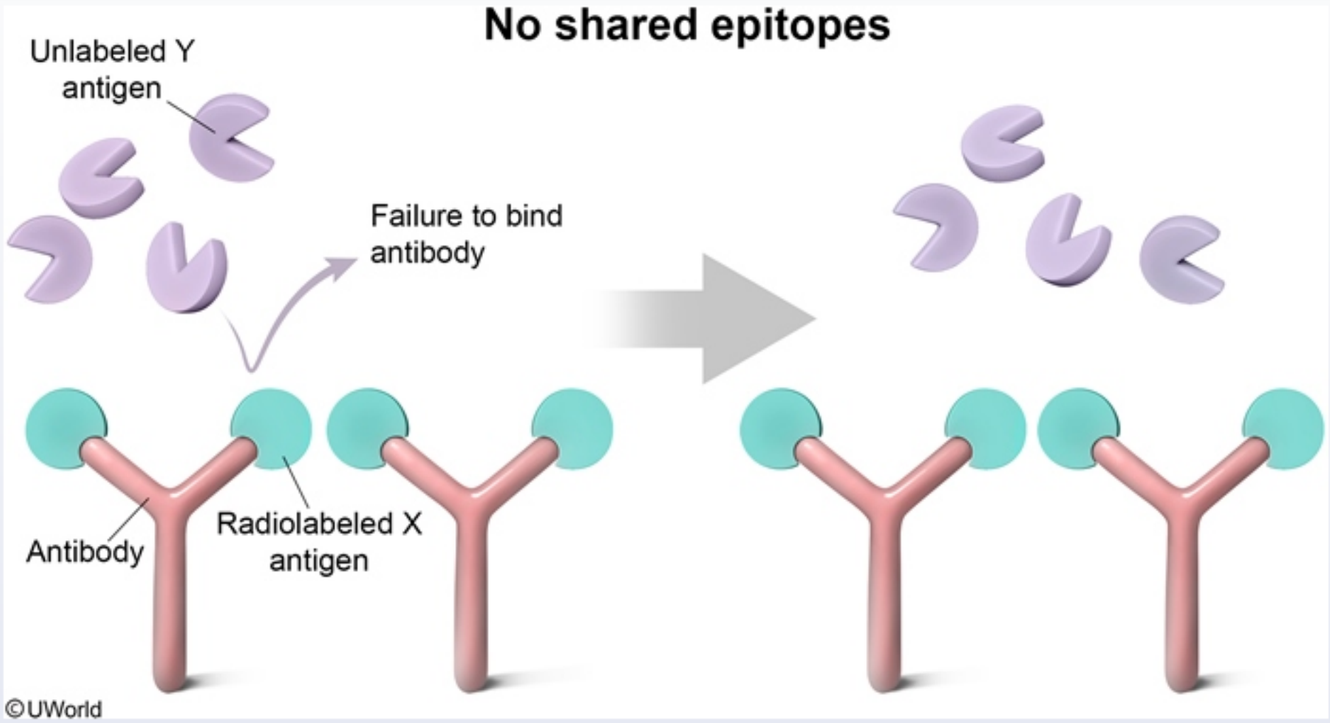

A **radioimmunoassay** is a laboratory technique that uses specific antibodies and a known quantity of radiolabeled antigen to determine the amount of antigen present in an unknown sample. In this technique, specific **antibodies** against a known antigen are attached to an assay plate. Next, a fixed quantity of **radiolabeled antigen** and varying quantities of **unlabeled antigen** are added to the plate. The system is subsequently washed to remove unbound antigens, and radioactivity is measured.

The researcher in the above experiment observes no change in radioactivity with increasing Y antigen concentrations. This indicates that antigen Y cannot bind the available antibodies and therefore **shares no epitopes** with antigen X.

(Choice B) If the radiolabeled and unlabeled antigens are identical (eg, have the same epitopes), they should compete equally for antibody binding sites. The amount of radiolabeled antigen displaced from the antibodies will be proportionate to the amount of unlabeled antigen added. Consequently, increasing concentrations of antigen Y would result in a proportionate decrease in measured radioactivity.

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A **radioimmunoassay** is a laboratory technique that uses specific antibodies and a known quantity of radiolabeled antigen to determine the amount of antigen present in an unknown sample. In this technique, specific **antibodies** against a known antigen are attached to an assay plate. Next, a fixed quantity of **radiolabeled antigen** and varying quantities of **unlabeled antigen** are added to the plate. The system is subsequently washed to remove unbound antigens, and radioactivity is measured.

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(Choices C and D) If antigen Y shared most or some of the epitopes of antigen X, then antigen Y would bind at a rate proportionate to both the amount of antibodies able to recognize the common epitopes and the amount of antigen Y added to the system.

Educational objective:
A radioimmunoassay uses specific antibodies and a fixed quantity of radiolabeled antigen to determine the amount of antigen present in an unknown sample. This is done by measuring the amount of radiolabeled antigen displaced from the antibodies in the system.

References

- Radioimmunoassay.
- Radioimmunoassay: review of basic principles.

Immunology	General Principles	Immunology principles
Subject	System	Topic

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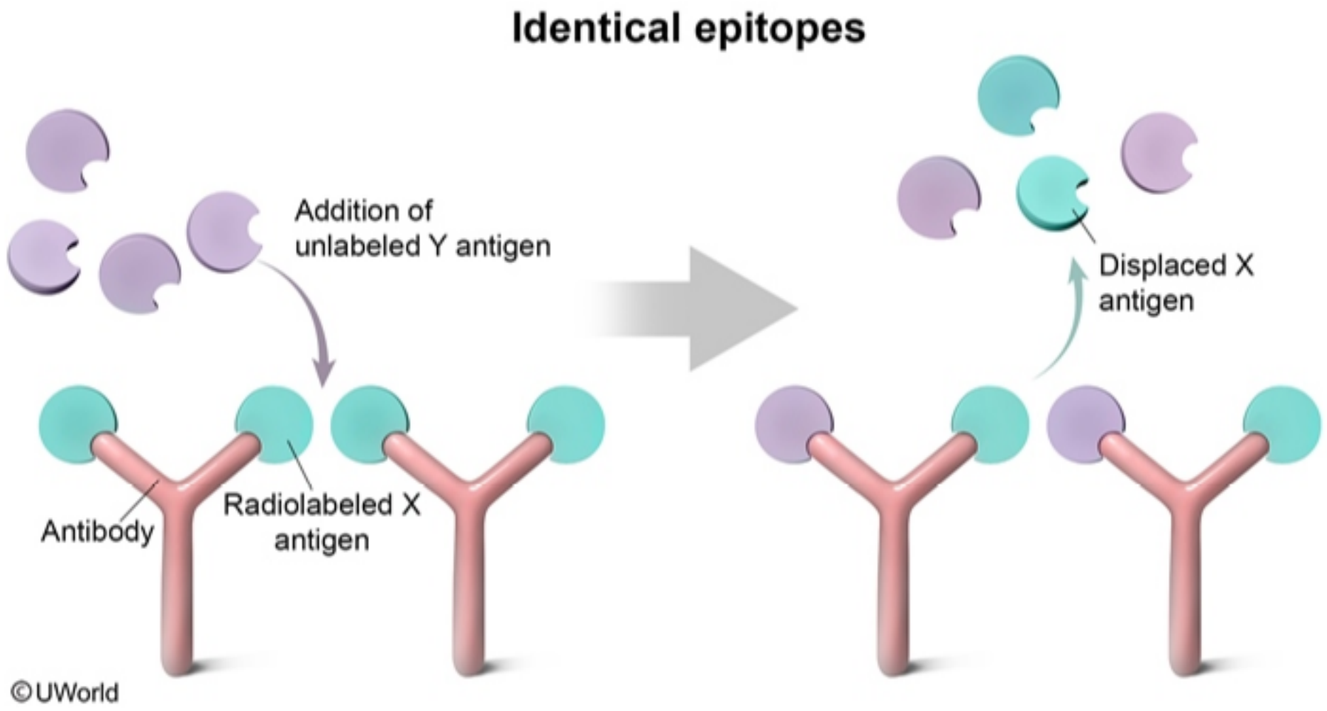

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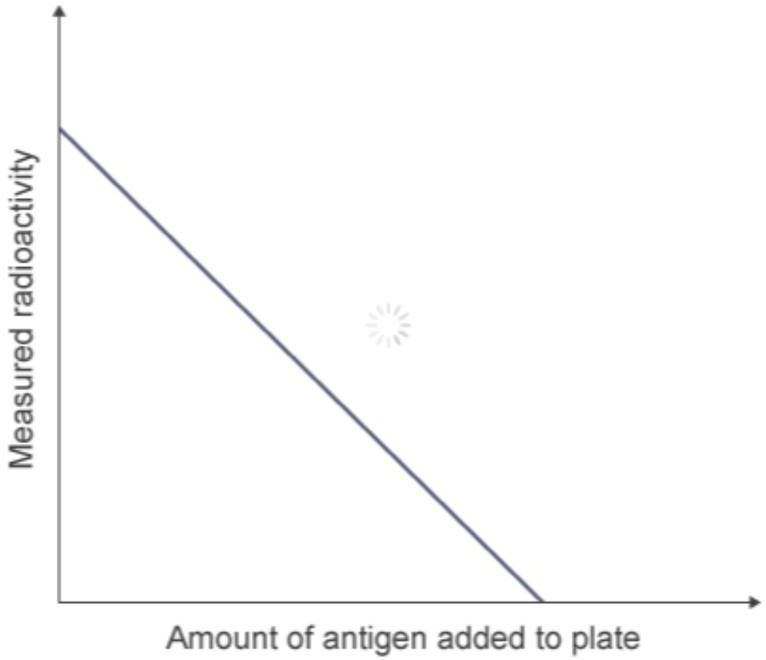

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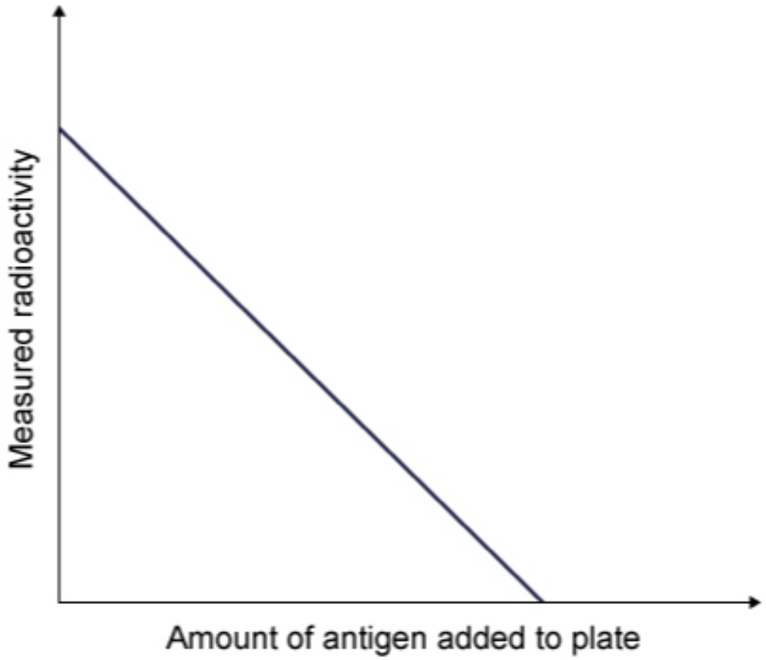

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A 37-year-old man comes to the emergency department because of increasing pain and tenderness in his right forearm. During a bar brawl 6 days earlier, he sustained a 4-cm laceration through the skin and subcutaneous tissue of his forearm. Treatment at the time of injury included cleaning and dressing the wound. Physical examination shows erythema surrounding the wound site and expression of yellow pus when pressure is applied adjacent to the wound. Which of the following molecules is most likely responsible for causing accumulation of pus over this patient's wound?

- A. Bradykinin
- B. C3a
- C. IL-3
- D. IL-8
- E. IL-10
- F. Leukotriene C_4

Submit

A 37-year-old man comes to the emergency department because of increasing pain and tenderness in his right forearm. During a bar brawl 6 days earlier, he sustained a 4-cm laceration through the skin and subcutaneous tissue of his forearm. Treatment at the time of injury included cleaning and dressing the wound. Physical examination shows erythema surrounding the wound site and expression of yellow pus when pressure is applied adjacent to the wound. Which of the following molecules is most likely responsible for causing accumulation of pus over this patient's wound?

- A. Bradykinin (1%)
- B. C3a (15%)
- C. IL-3 (3%)
- ✓ D. IL-8 (65%)
- E. IL-10 (5%)
- F. Leukotriene C_4 (8%)

Omitted
Correct answer
D

65%
Answered correctly

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Explanation

Neutrophil chemotaxis

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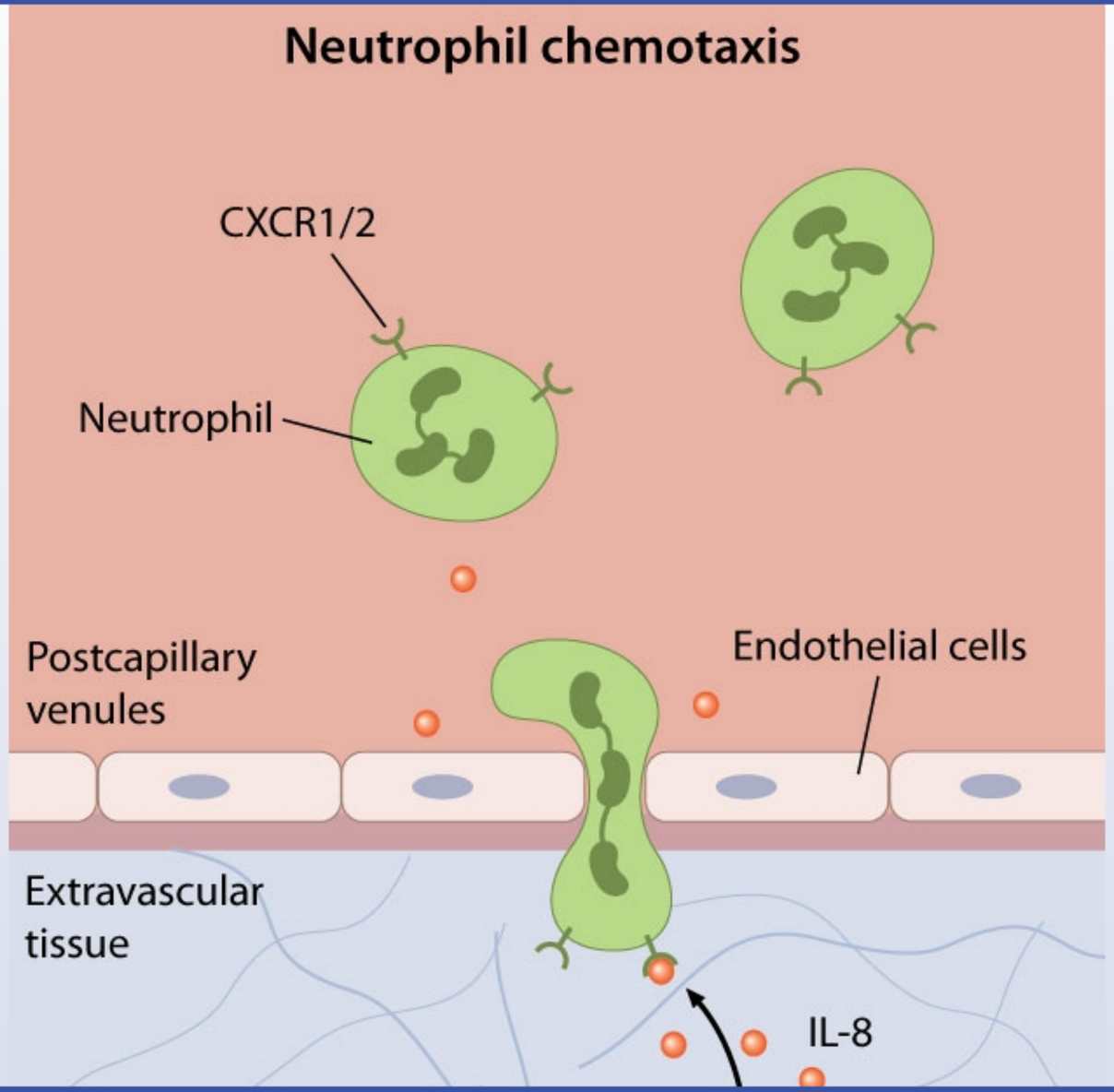

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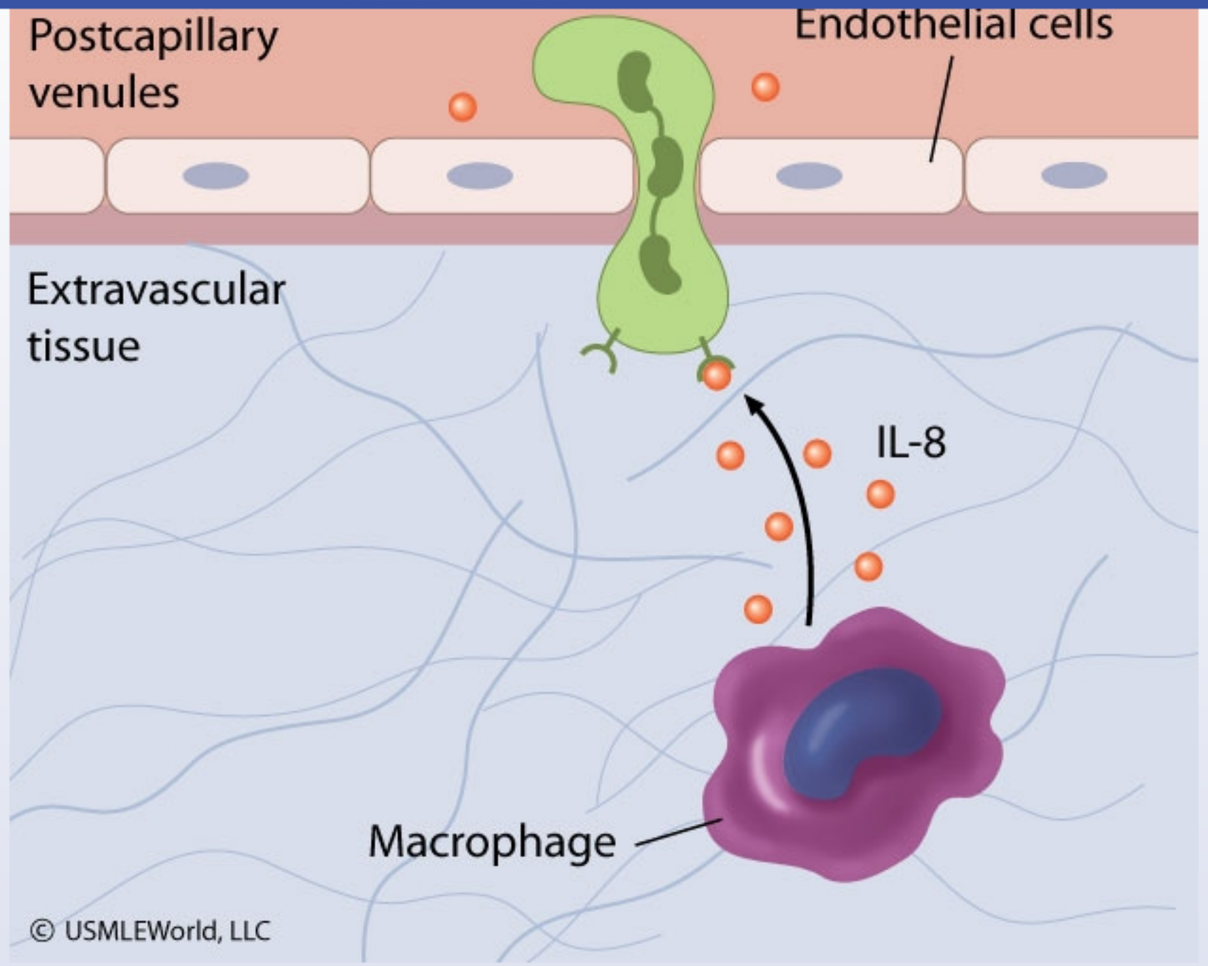

Pus consists of a thin, protein-rich fluid, known as liquor puris, and dead leukocytes, primarily neutrophils. During infection, macrophages and surrounding endothelial cells release cytokines such as **interleukin-8** (IL-8) that trigger **neutrophils** to enter the site of infection via **chemotaxis**. IL-8 also induces phagocytosis in neutrophils once they have arrived.

(Choice A) Bradykinin is a component of the kinin system. It causes vasodilation, increases vascular permeability, stimulates nonvascular

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Pus consists of a thin, protein-rich fluid, known as liquor puris, and dead leukocytes, primarily neutrophils. During infection, macrophages and surrounding endothelial cells release cytokines such as **interleukin-8** (IL-8) that trigger **neutrophils** to enter the site of infection via **chemotaxis**. IL-8 also induces phagocytosis in neutrophils once they have arrived.

(Choice A) Bradykinin is a component of the kinin system. It causes vasodilation, increases vascular permeability, stimulates nonvascular smooth muscle contraction, and mediates pain.

(Choice B) C3a is a component of the complement system. C3a, C4a, and C5a are inflammatory anaphylatoxins that trigger histamine release from mast cells, resulting in vasodilation and enhanced vascular permeability. C5a also recruits and activates neutrophils, monocytes, eosinophils, and basophils. In contrast, C3a recruits and activates eosinophils and basophils, but not neutrophils.

(Choice C) IL-3 is a cytokine produced by activated T cells. It stimulates the growth and differentiation of stem cells in the bone marrow.

(Choice E) IL-10 is an anti-inflammatory cytokine produced by T_H2 cells and macrophages. IL-10 limits the production of pro-inflammatory cytokines (eg, gamma interferon, IL-2, IL-3, and TNF-α).

(Choice F) Leukotriene C_4 (and its relatives, leukotriene D_4 and E_4) triggers intense vasoconstriction, increased vascular permeability, and bronchospasm. Leukotriene B_4 and the leukotriene precursor 5-HETE stimulate neutrophil migration to the site of inflammation (but not leukotriene C_4).

Educational objective:
Interleukin-8 is a chemokine produced by macrophages that induces chemotaxis and phagocytosis in neutrophils. Other significant chemotactic agents include leukotriene B_4, 5-HETE (the leukotriene precursor), and complement component C5a.

Immunology	Allergy & Immunology	Inflammation
Subject	System	Topic

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Educational objective:
Interleukin-8 is a chemoki
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Cytokine	Major source	Major effects
IL-1	Macrophages	• ↑ Neutrophil & macrophage migration • ↑ Acute-phase reactants, fever & shock
IL-2	T cells	• ↑ T-cell activation & proliferation • ↑ NK cell & macrophage activity • ↑ B-cell growth
IL-3	T cells	• ↑ Hematopoiesis
IL-4	T_H2 cells	• ↑ T_H2-cell differentiation • ↑ B-cell growth • ↑ Isotype switching to IgE
IL-5	T_H2 cells	• ↑ Differentiation of eosinophils • ↑ Isotype switching to IgA
IL-6	Macrophages	• ↑ T- & B-cell growth • ↑ Osteoclast activity • ↑ Acute-phase reactants & fever
IL-8	Macrophages T cells	• ↑ Neutrophil activation & chemotaxis

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Cytokine	Major source	Major effects
IL-1	Macrophages	• ↑ Neutrophil & macrophage migration • ↑ Acute-phase reactants, fever & shock
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IL-5	T_H2 cells	• ↑ Differentiation of eosinophils • ↑ Isotype switching to IgA
IL-6	Macrophages	• ↑ T- & B-cell growth • ↑ Osteoclast activity • ↑ Acute-phase reactants & fever
IL-8	Macrophages T cells	• ↑ Neutrophil activation & chemotaxis
IL-10	T_H2 cells	• ↓ T_H1-cell differentiation • ↓ Cell-mediated immunity & APC activity • ↑ B-cell function
IL-12	Macrophages	• ↑ T_H1-cell differentiation • ↑ NK-cell & CD8+ T-cell activity
IFN-gamma	T_H1 cells NK cells	• ↑ Intracellular killing by macrophages • ↑ MHC class I & II expression

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Educational objective:
Interleukin-8 is a chemoki
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Immunology — Subject
Allerg — System

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		• ↑ Isotype switching to IgE
IL-5	T_H2 cells	• ↑ Differentiation of eosinophils • ↑ Isotype switching to IgA
IL-6	Macrophages	• ↑ T- & B-cell growth • ↑ Osteoclast activity • ↑ Acute-phase reactants & fever
IL-8	Macrophages T cells	• ↑ Neutrophil activation & chemotaxis
IL-10	T_H2 cells	• ↓ T_H1-cell differentiation • ↓ Cell-mediated immunity & APC activity • ↑ B-cell function
IL-12	Macrophages	• ↑ T_H1-cell differentiation • ↑ NK-cell & CD8+ T-cell activity
IFN-gamma	T_H1 cells NK cells	• ↑ Intracellular killing by macrophages • ↑ MHC class I & II expression • ↑ T_H1-cell differentiation
TGF-beta	Most cell types	• ↓ Immune cell function • ↑ Matrix synthesis & angiogenesis
GM-CSF	T cells Macrophages	• ↑ Growth & differentiation of myeloid progenitors
TNF-alpha	Macrophages	• ↑ Inflammation & cell-mediated immunity • ↑ Acute-phase reactants, fever & shock

APC = antigen-presenting cell; **GM-CSF** = granulocyte-macrophage colony-stimulating factor; **IFN** = interferon; **MHC** = major histocompatibility complex; **NK** = natural killer; **TGF** = tumor growth factor; **TNF** = tumor necrosis factor.

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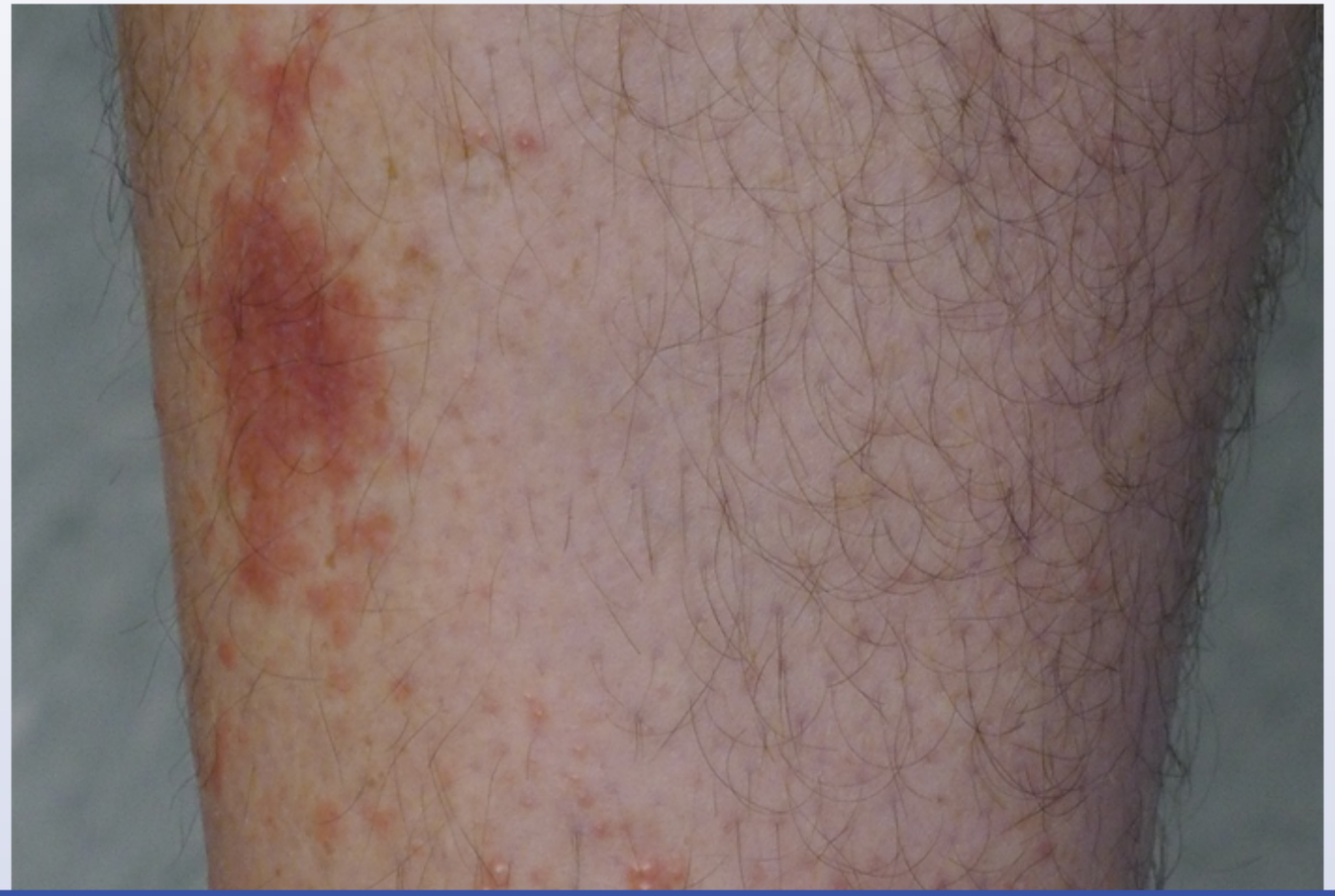
A 34-year-old electric company worker comes to the physician with a skin rash on his right leg. He has not eaten any new foods or changed detergents, soaps, or lotions. On further questioning, the patient recalls that he recently worked on a repair job in an unmaintained, wooded area. He had atopic dermatitis as a child but no other significant illnesses. On physical examination, he appears uncomfortable and is constantly scratching his leg. His lungs are clear bilaterally and his heart sounds are normal. Examination of his right leg shows the findings in the image below.



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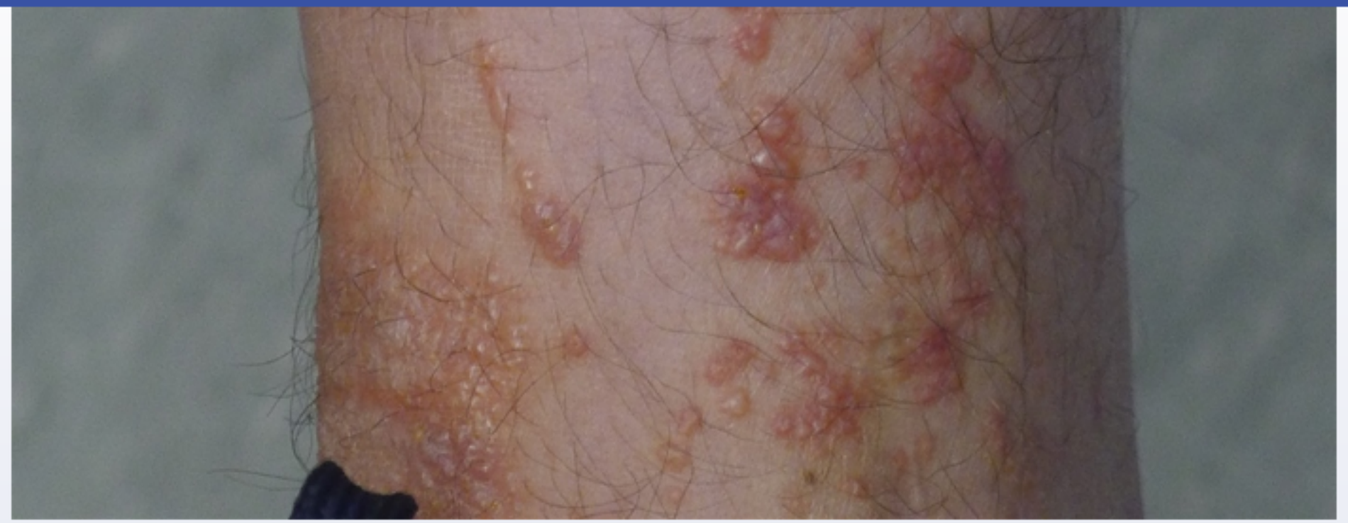

Which of the following cells is most responsible for causing the tissue damage seen in this patient?

- A. Basophils
- B. Eosinophils
- C. Mast cells
- D. Neutrophils
- E. Plasma cells
- F. T lymphocytes

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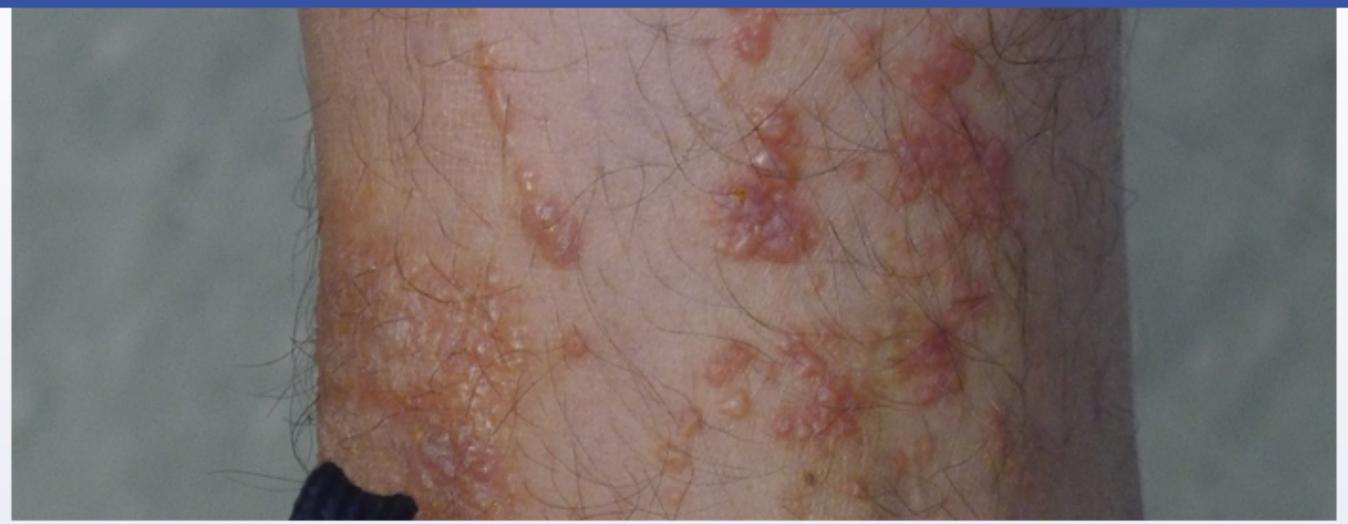

Which of the following cells is most responsible for causing the tissue damage seen in this patient?

A. Basophils (1%)
B. Eosinophils (9%)
C. Mast cells (25%)
D. Neutrophils (2%)
E. Plasma cells (1%)
✓ F. T lymphocytes (60%)

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Correct answer

60%
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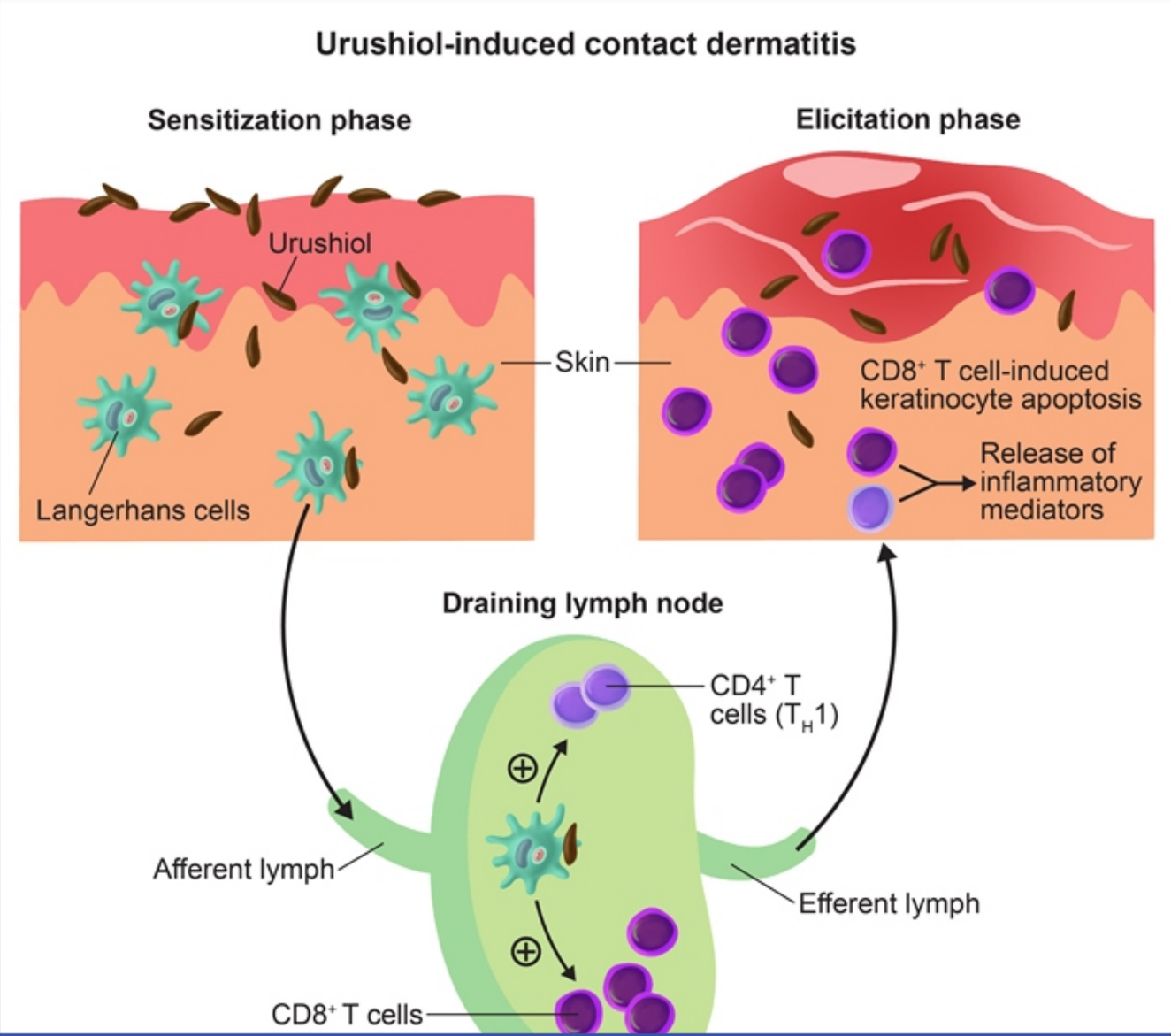

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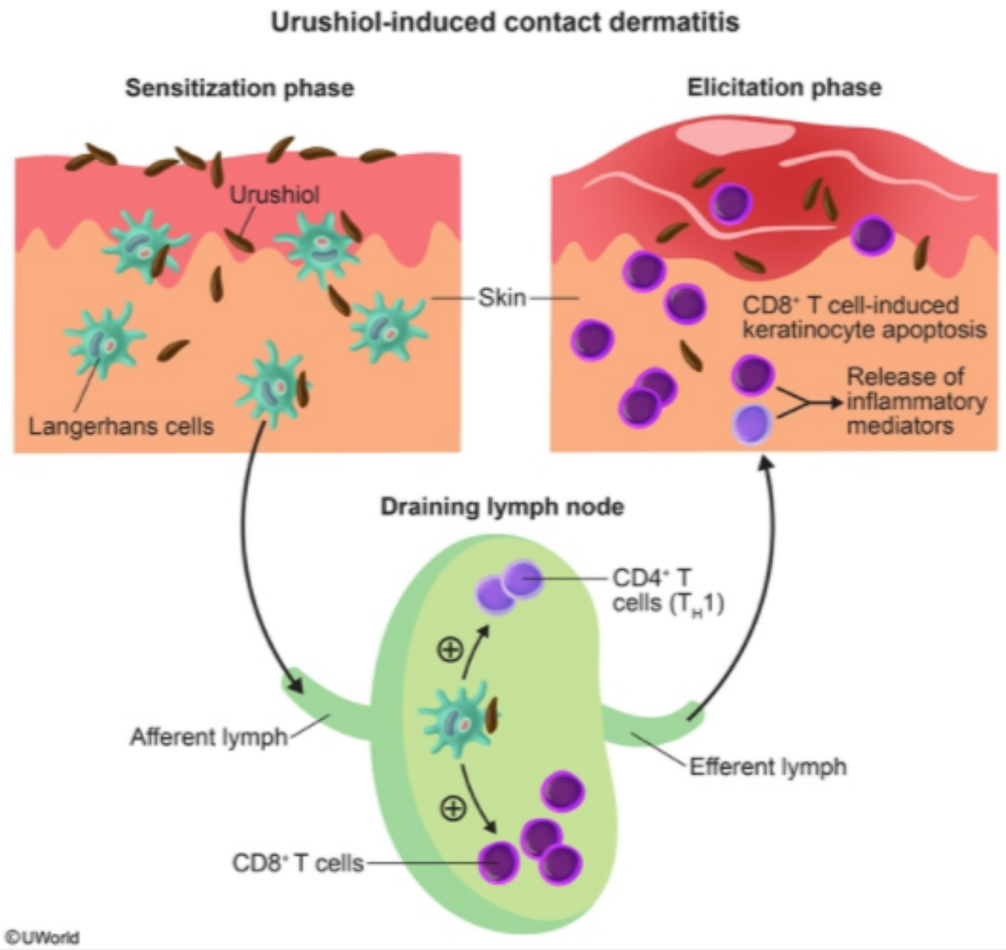

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This patient's pruritic skin rash following wilderness exposure is consistent with **poison ivy dermatitis**, a form of contact dermatitis. Poison ivy, poison oak, and poison sumac all produce **urushiol**, a small allergenic substance that causes an immune response when attached to proteins (ie, a hapten). Following contact with these plants, patients develop a **highly pruritic**, erythematous rash consisting of papules, vesicles, and bullae that may show signs of excoriation. The rash most frequently affects exposed skin (eg, legs, forearms) and often forms **linear streaks** as the patient walks past the plant, dragging it along the skin.

Contact dermatitis is a type IV (**delayed-type**) hypersensitivity reaction that occurs in 2 distinct phases:

1. The **sensitization phase** leads to the creation of hapten-specific T cells and takes 10-14 days. Cutaneous dendritic cells take up the haptens and express them on MHC-I and MHC-II molecules as hapten-conjugated peptides. These dendritic cells travel to the draining lymph nodes and interact with hapten-sensitive CD4+ and CD8+ T cells, causing activation and clonal expansion.
2. The **elicitation phase** occurs within 2-3 days following re-exposure to the same antigen (or following sensitization after first exposure to a highly antigenic antigen such as urushiol). In this phase, the hapten is taken up by skin cells and causes activation of hapten-sensitized T cells in the dermis and epidermis. This results in an inflammatory response and the clinical manifestations of contact dermatitis.

Depending on the etiologic agent, contact dermatitis can be mediated primarily by cytotoxic CD8+ T cells or CD4+ T_H1 cells (that cause indirect damage by activating macrophages). In urushiol-induced contact dermatitis, **CD8+ T cells** are the primary effector cells and directly destroy keratinocytes expressing haptenated proteins.

(Choices A and C) Mast cells and basophils, along with IgE, are primarily responsible for type I hypersensitivity allergic reactions. Mast cells play a role in modulating the response in contact dermatitis by affecting antigen presentation and T-cell recruitment and activation, but they are not the main effector cells in type IV hypersensitivity.

(Choice B) Eosinophils are cells that play a role in the defense against parasitic organisms and allergic reactions.

(Choice D) Neutrophils are the primary phagocytic killers of the innate immune system and do not play a significant role in type IV hypersensitivity reactions. They are more important in type III hypersensitivity reactions, in which deposited immune complexes activate complement and cause neutrophil-mediated tissue damage.

(Choice E) Plasma cells are the principal cells responsible for the synthesis of immunoglobulins, which are directly responsible for type II and III hypersensitivity reactions.

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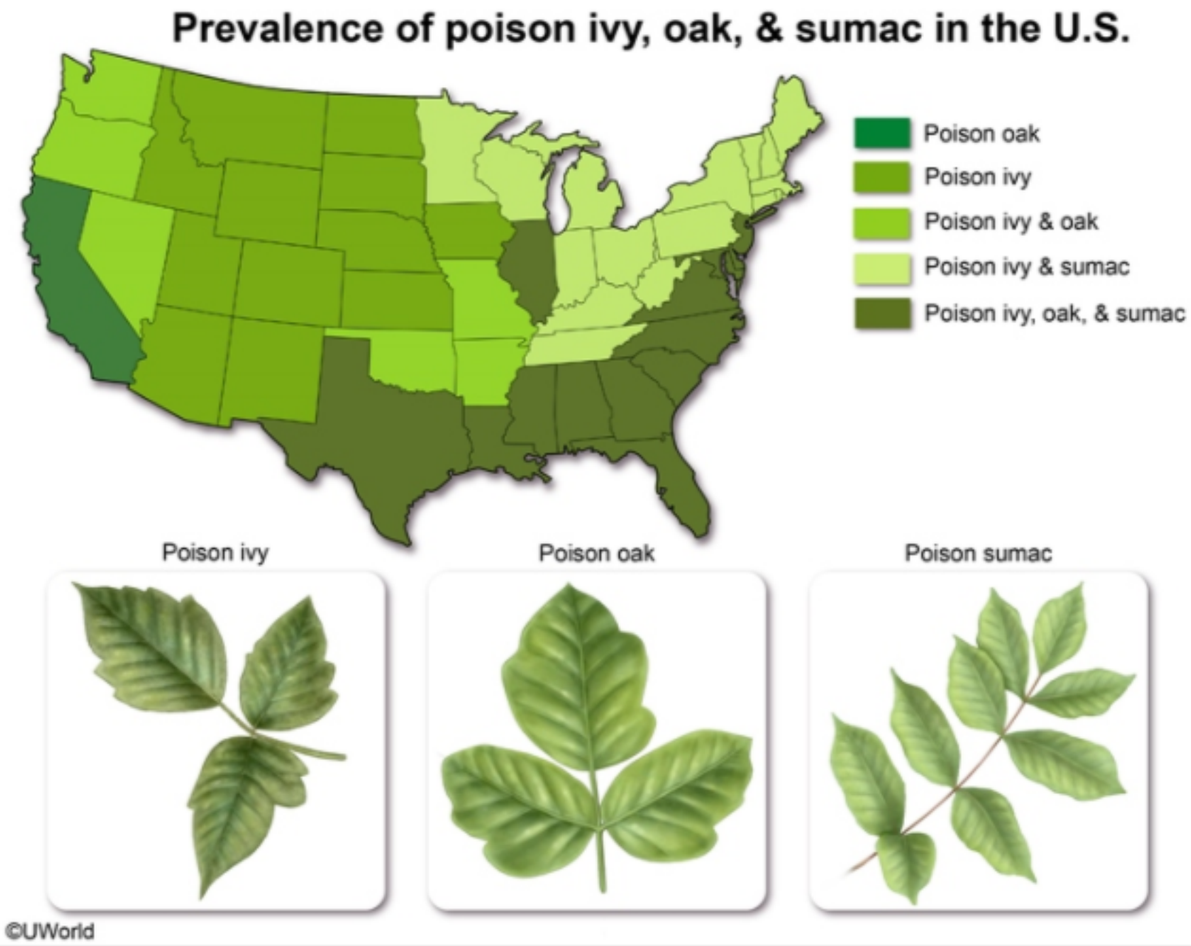

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(Choice E) Plasma cells are the principal cells responsible for the synthesis of immunoglobulins, which are directly responsible for type II and III hypersensitivity reactions.

Educational objective:
Poison ivy dermatitis is a form of allergic contact dermatitis, which is a type IV hypersensitivity reaction mediated primarily by T lymphocytes. It manifests as intensely pruritic erythematous papules, vesicles, or bullae that often form linear patterns.

References

- Contribution of CD4(+)and CD8(+) T-cells in contact hypersensitivity and allergic contact dermatitis.
- The role of CD4+ and CD8+ T cells in contact hypersensitivity and allergic contact dermatitis.
- Allergic contact dermatitis.

A 63-year-old man comes to the physician after noticing a reddish tinge to his urine for the last couple of days. During evaluation of his hematuria, an abdominal CT scan reveals a left-sided renal mass. Further workup also shows multiple pulmonary and bone nodules. CT-guided biopsy of a peripherally located lung nodule demonstrates renal cell carcinoma. High-dose interleukin-2 (IL-2) is started, and 4 weeks later there is a significant reduction in his tumor burden. Which of the following mechanisms was most likely responsible for regression of his malignancy?

A. Anti-angiogenic effect of IL-2

B. Direct cytotoxic effect of IL-2 on the tumor cells

C. Enhanced activity of natural killer cells

D. IL-2-induced apoptosis of tumor cells

E. Increased expression of MHC Class 1 on tumor cells

Submit

A 63-year-old man comes to the physician after noticing a reddish tinge to his urine for the last couple of days. During evaluation of his hematuria, an abdominal CT scan reveals a left-sided renal mass. Further workup also shows multiple pulmonary and bone nodules. CT-guided biopsy of a peripherally located lung nodule demonstrates renal cell carcinoma. High-dose interleukin-2 (IL-2) is started, and 4 weeks later there is a significant reduction in his tumor burden. Which of the following mechanisms was most likely responsible for regression of his malignancy?

- A. Anti-angiogenic effect of IL-2 (4%)
- B. Direct cytotoxic effect of IL-2 on the tumor cells (9%)
- ✓ C. Enhanced activity of natural killer cells (54%)
- D. IL-2-induced apoptosis of tumor cells (13%)
- E. Increased expression of MHC Class 1 on tumor cells (17%)

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Correct answer
C

54%
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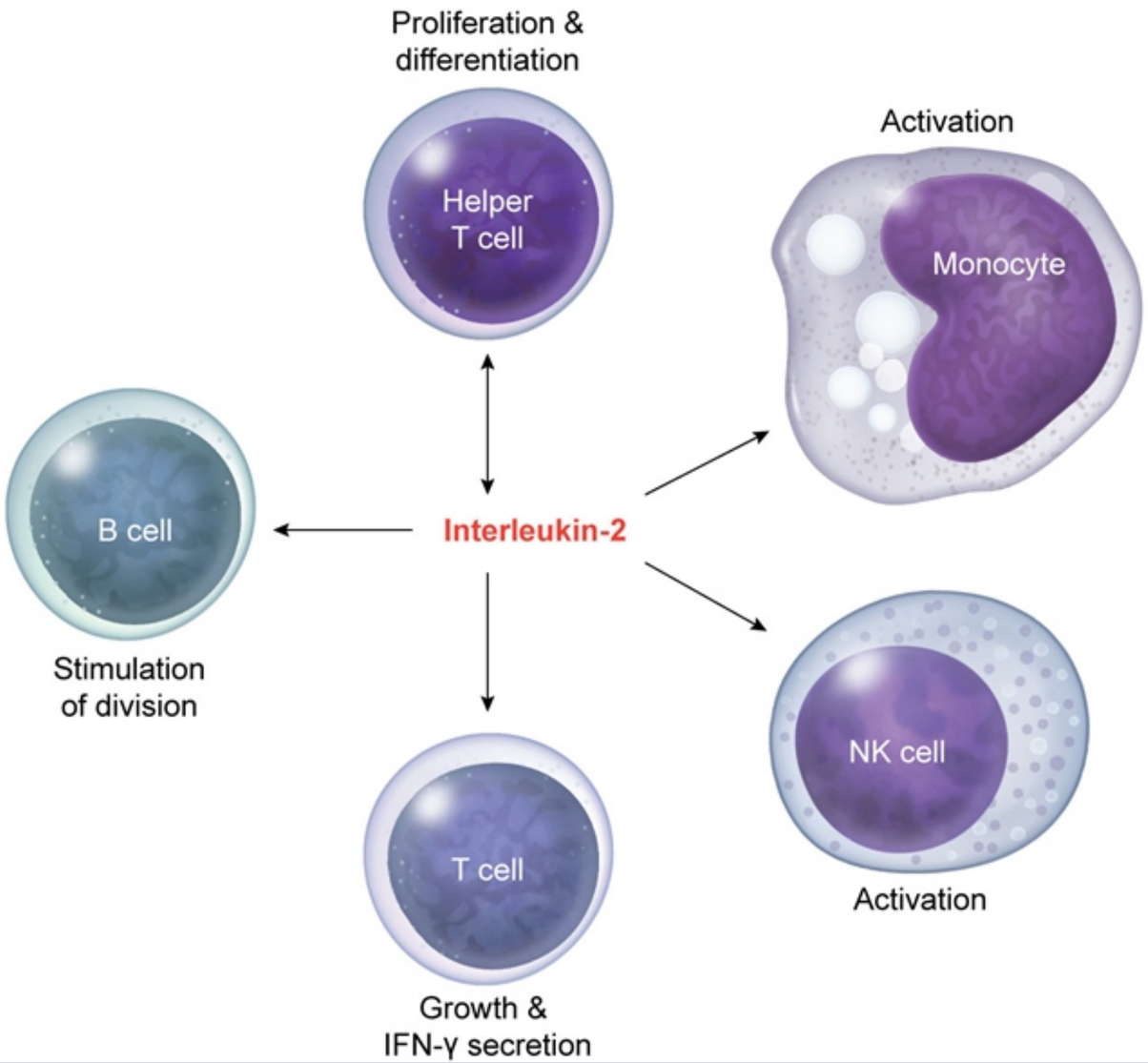
Effects of interleukin-2



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Effects of interleukin-2

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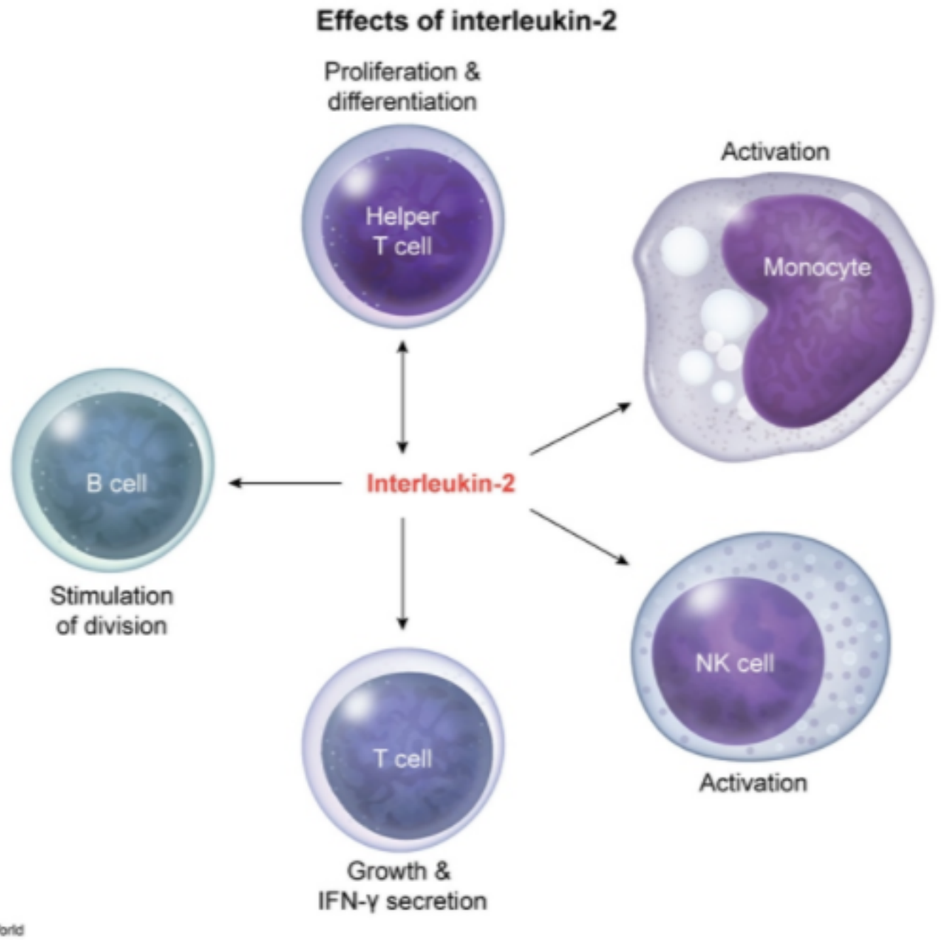

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IFN-γ secretion

Interleukin-2 (IL-2) is produced primarily by helper T cells and is the major growth factor for T lymphocytes. Antigen binding to the T cell receptor stimulates the secretion of IL-2 and the expression of IL-2 receptors (IL-2R). The IL-2/IL-2R (autocrine) interaction then stimulates the growth, differentiation, and survival of antigen-specific CD4+ T cells and CD8+ T cells. IL-2 also promotes the growth of B cells and activates natural killer (NK) cells and monocytes.

Increased activity of T cells and NK cells is thought to be responsible for IL-2's anti-tumor effects. IL-2 (aldesleukin) is currently used as immunotherapy for metastatic melanoma and renal cell carcinoma. The IL-2-induced immune response against renal cell carcinoma results in tumor regression in approximately 10% of patients. These responses can persist for many years, and the majority of complete responders remain free of long-term relapses.

(Choice A) A marked increase in vascular endothelial growth factor (VEGF) expression is thought to play a role in tumor angiogenesis. Bevacizumab, a humanized monoclonal antibody, interferes with VEGF receptor activation, thereby inhibiting angiogenesis.

(Choice B) Alemtuzumab, an anti-CD52 humanized monoclonal antibody, is used for treatment of chronic lymphocytic leukemia. On binding to CD52, alemtuzumab initiates a direct cytotoxic effect through complement fixation and antibody-dependent, cell-mediated cytotoxicity.

(Choice D) Chemotherapeutic agents (eg, etoposide, vincristine, and cyclophosphamide) are able to kill cancer cells by inducing apoptosis.

(Choice E) Interferon-gamma increases expression of MHC class I & II, improving antigen presentation in all cells.

Educational objective:
Interleukin-2 (IL-2) is produced by helper T cells and stimulates the growth of CD4+ and CD8+ T cells and B cells. IL-2 also activates natural killer cells and monocytes. The increased activity of T cells and natural killer cells is thought to be responsible for IL-2's anti-cancer effect on metastatic melanoma and renal cell carcinoma.

References

- Role of immunotherapy for renal cell cancer in 2011.

Immunology	General Principles	Cytokines
Subject	System	Topic

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Interleukin 2 (IL-2) is produced primarily by helper T cells and is the major growth factor for T lymphocytes. Antigen binding to the T cell receptor

Exhibit Display

Interleukin	Major source	Major effects
IL-1	Macrophages	• ↑Neutrophil & macrophage migration • ↑Acute phase reactants, fever & shock
IL-2	T cells	• ↑T cell activation & proliferation • ↑NK cell & macrophage activity • ↑B cell growth
IL-3	T cells	• ↑Hematopoiesis
IL-4	T_H2 cells	• ↑T_H2 cell differentiation • ↑B cell growth • ↑Isotype switching to IgE
IL-5	T_H2 cells	• ↑Differentiation of eosinophils • ↑Isotype switching to IgA
IL-6	Macrophages	• ↑T and B cell growth • ↑Osteoclast activity • ↑Acute phase reactants & fever
IL-8	Macrophages T cells	• ↑Neutrophil activation & chemotaxis
IL-10	T_H2 cells	• ↓TH1 cell differentiation • ↓Cell-mediated immunity & APC activity • ↑B cell function
IL-12	Macrophages	• ↑TH1 cell differentiation • ↑NK cell & CD8+ T cell activity

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A 26-year-old man comes to the office due to myalgia, nasal congestion, and cough. Temperature is 38.3 C (100.9 F). Examination shows nasal and pharyngeal hyperemia. Rapid influenza antigen testing of nasopharyngeal secretions is positive. Within the infected cells of the patient's respiratory tract, viral proteins are degraded and attached to major histocompatibility complex class I molecules, which are then expressed on the cell surface for presentation to cytotoxic $CD8^+$ lymphocytes. Which of the following enzymes is most essential to initiating this process?

A. Acid phosphatase
B. Caspase
C. Guanylate cyclase
D. Myeloperoxidase
E. Ubiquitin ligase

Submit

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A. Acid phosphatase (14%)
B. Caspase (20%)
C. Guanylate cyclase (5%)
D. Myeloperoxidase (13%)
✓ E. Ubiquitin ligase (46%)

Omitted
Correct answer
E

46%
Answered correctly

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Explanation

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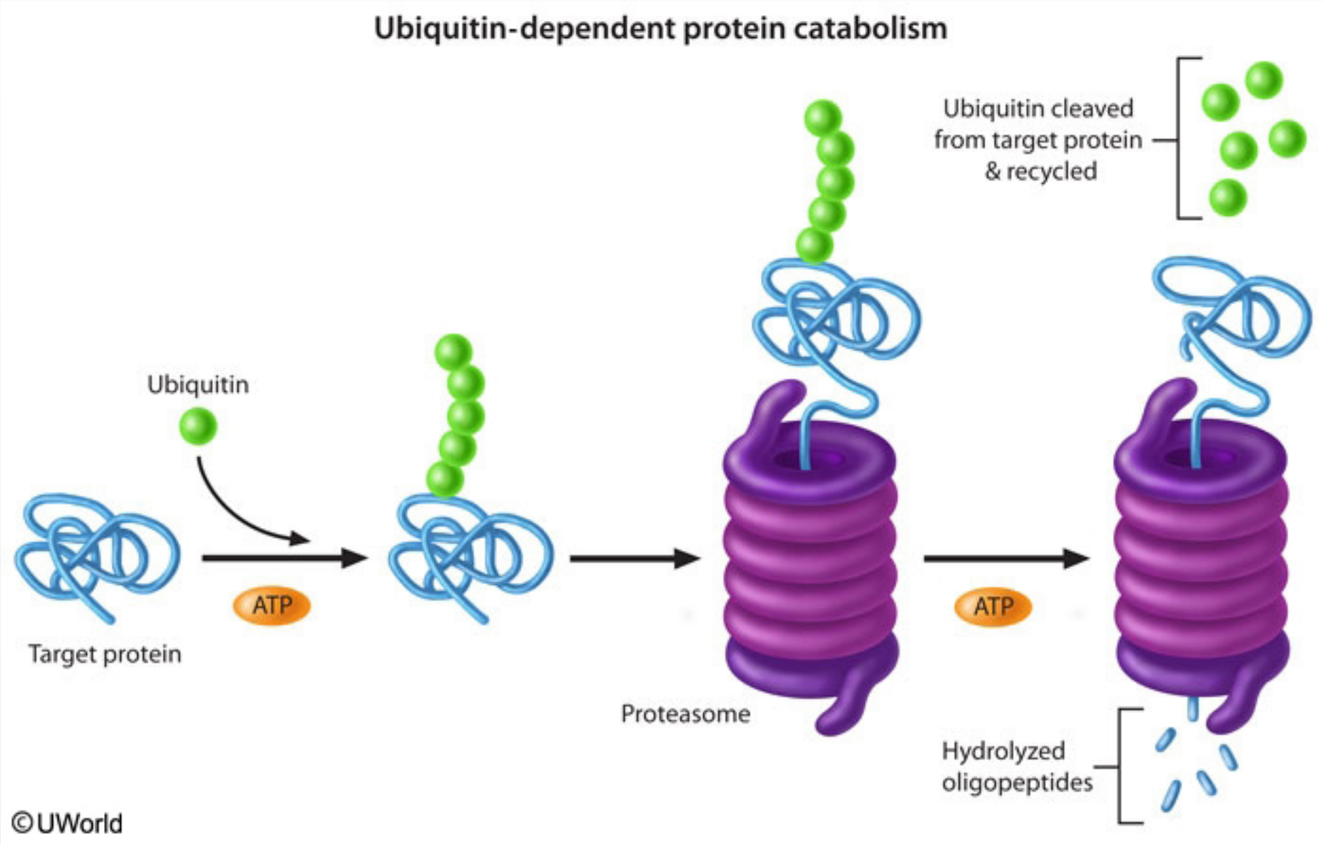

The cellular immune response to a viral pathogen (eg, influenza) requires the presentation of viral antigens to effector immune cells (eg, $CD8^+$ lymphocytes). The **ubiquitin proteasome pathway** (UPP) is essential to this process because of its role in breaking down native and foreign intracellular proteins. **Ubiquitin ligase** initiates the UPP by recognizing specific protein substrates and catalyzing the attachment of ubiquitin. The proteins tagged with ubiquitin are then **broken down** by a proteasome to peptide fragments which can be recycled into amino acids.

The **peptide fragments** produced during this process can also be coupled to major histocompatibility complex (MHC) class I molecules in the endoplasmic reticulum and then presented on the cell surface. **Cytotoxic $CD8^+$ lymphocytes** recognize nonnative (eg, viral) proteins on infected

The cellular immune response to a viral pathogen (eg, influenza) requires the presentation of viral antigens to effector immune cells (eg, $CD8^+$ lymphocytes). The **ubiquitin proteasome pathway** (UPP) is essential to this process because of its role in breaking down native and foreign intracellular proteins. **Ubiquitin ligase** initiates the UPP by recognizing specific protein substrates and catalyzing the attachment of ubiquitin. The proteins tagged with ubiquitin are then **broken down** by a proteasome to peptide fragments which can be recycled into amino acids.

The **peptide fragments** produced during this process can also be coupled to major histocompatibility complex (MHC) class I molecules in the endoplasmic reticulum and then presented on the cell surface. **Cytotoxic $CD8^+$ lymphocytes** recognize nonnative (eg, viral) proteins on infected cells and trigger **apoptosis** of the cell by activating the caspase cascade through the release perforin and granzyme **(Choice B)**.

(Choice A) Acid phosphatase is found in the lysosome of most cells and hydrolyzes organic phosphates, but it is not involved in antigen presentation.

(Choice C) Guanylate cyclase is involved in the G-protein signaling cascade, which plays a crucial role in the activation and regulation of diverse physiologic processes (eg, smooth muscle relaxation, retinal phototransduction).

(Choice D) Myeloperoxidase is a key component of the respiratory burst of neutrophils and is released into the phagocytic vacuole and extracellular space as part of the immune response to bacteria and other pathogens.

Educational objective:
An essential step in the activation of the cellular immune response to a virus is the breakdown of intracellular viral proteins by the ubiquitin proteasome pathway. This pathway is initiated by ubiquitin ligases, which recognize specific protein substrates and attach a ubiquitin tag. The target proteins are then degraded by a proteasome into peptide fragments, which are coupled with major histocompatibility complex class I proteins and presented on the cell surface for surveillance by cytotoxic $CD8^+$ lymphocytes.

References

- The ubiquitin-proteasome system and its role in inflammatory and autoimmune diseases.

Immunology	General Principles	Ubiquitin proteasome pathway
Subject	System	Topic

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The cellular immune response to a viral pathogen (eg, influenza) requires the presentation of viral antigens to effector immune cells (eg, CD8+

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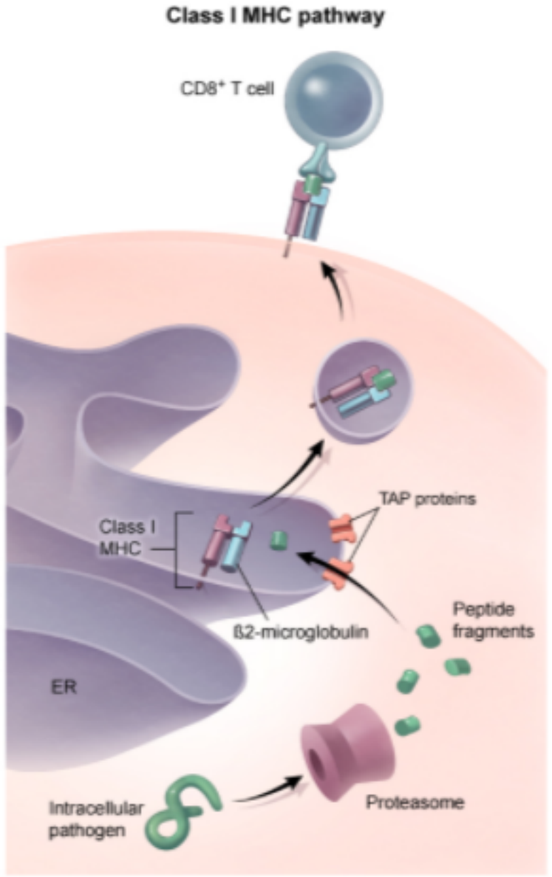

ER = endoplasmic reticulum; MHC = major histocompatibility complex; TAP = transporter associated with antigen processing.

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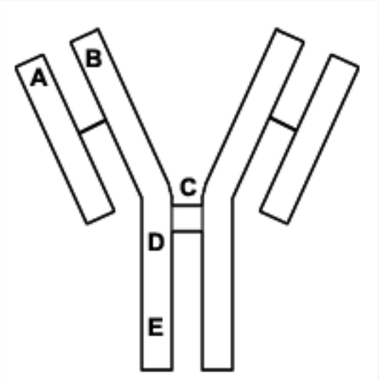
The immune response observed in an apparently healthy 12-year-old Caucasian male after recurrent exposure to a bacterial antigen is characterized by rapid increase in serum IgG level. Some immunoglobulin molecules are attached to the surface of macrophages, neutrophils and B lymphocytes. Which of the following is the cell attachment site for the immunoglobulin molecule shown on the slide below?



A. A
B. B
C. C
D. D
E. E

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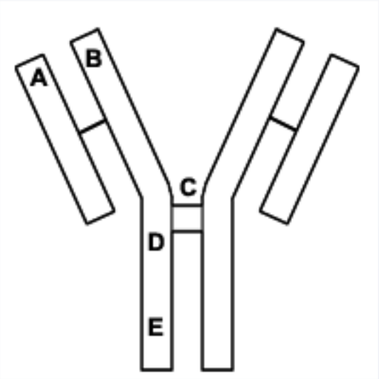

A. A (5%)
B. B (5%)
C. C (2%)
D. D (8%)
✓ E. E (77%)

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Correct answer
E

77%
Answered correctly

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02/03/2020
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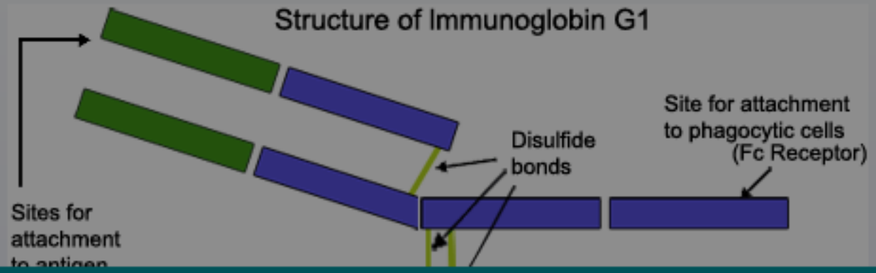
Explanation



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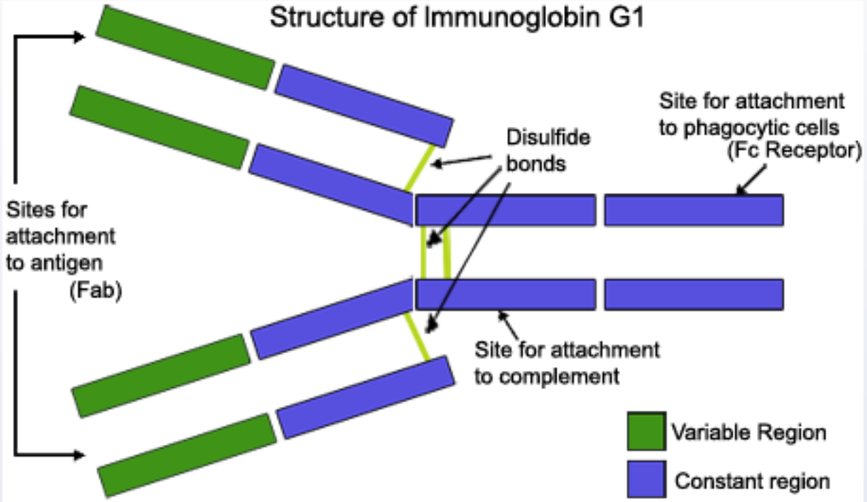
Close

specifically to the Fc portion of IgG molecules. This binding is essential for the process of opsonization. Opsonization refers to the promotion of phagocytosis of tagged material by phagocytic cells such as neutrophils and macrophages. IgG acts as an opsonin by binding antigens (i.e. bacterial surface proteins, etc.) at its Fab sites and subsequently binding a phagocyte at its Fc site. This signals for the phagocytosis of the Fab bound antigen by the phagocyte. The Fc region of the immunoglobulin molecule near the carboxy terminal **(Choice E)** is the attachment site to Fc receptors. A similar process occurs with IgE antibody in type I hypersensitivity reactions. IgE binds allergenic antigen at its Fab sites and binds Fc receptors on mast cells and basophils. Once multiple IgE molecules bind antigen and the Fc receptor on the mast cell or basophil and subsequently cross-link with each other, these cells will degranulate thereby releasing multiple vasoactive substances into the local milieu.

(Choices A and B) Choices A and B indicate the hypervariable regions of the Fab (antigen binding fragment) portion of the light chain and heavy chain of the IgG molecule, respectively. These regions of the immunoglobulin protein are also referred to as the complementarity-determining regions of the antibody because their structure determines what complementary protein antigen will be bound by the antibody.

Explanation



The basic IgG immunoglobulin structure is pictured above, and the question asks for the identification of the part of the immunoglobulin that binds receptors on macrophages, neutrophils and B-lymphocytes. These cell types express cell surface proteins known as Fc receptors (FcR) that bind specifically to the Fc portion of IgG molecules. This binding is essential for the process of opsonization. Opsonization refers to the promotion of phagocytosis of tagged material by phagocytic cells such as neutrophils and macrophages. IgG acts as an opsonin by binding antigens (i.e. bacterial surface proteins, etc.) at its Fab sites and subsequently binding a phagocyte at its Fc site. This signals for the phagocytosis of the Fab bound antigen by the phagocyte. The Fc region of the immunoglobulin molecule near the carboxy terminal **(Choice E)** is the attachment site to Fc receptors. A similar process occurs with IgE antibody in type I hypersensitivity reactions. IgE binds allergenic antigen at its Fab sites and binds Fc receptors on mast cells and basophils. Once multiple IgE molecules bind antigen and the Fc receptor on the mast cell or basophil and subsequently cross-link with each other, these cells will degranulate thereby releasing multiple vasoactive substances into the local milieu.

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(Choice C) The area indicated by the letter C represents the two disulfide bonds that hold the heavy chains of the immunoglobulin together just before the hinge region of the molecule.

(Choice D) The region marked by the letter D indicates the complement binding site on the IgG molecule; the complement binding site is in approximately the same location on an IgM molecule, but recall that IgM circulates in pentameric form. The classical complement pathway is triggered by the binding of the C1 complement component to two molecules of either IgM or IgG after these immunoglobulins have bound circulating antigen such as a bacterium.

Educational Objective:
The carboxy terminal of the Fc portion of the heavy immunoglobulin chains represents the site that binds to the Fc receptors on neutrophils and macrophages. Antibody bound to antigen is able to signal for the phagocytosis of that antigen by a conformational change of the Fc region allowing binding to the Fc receptor on phagocytes. This leads to subsequent phagocytosis of the organism / antibody complex and subsequent destruction of the organism.

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Immunology	General Principles	Immunoglobulins
Subject	System	Topic

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Preventive disease specialists working in a developing country are investigating vaccination options to limit the spread of poliomyelitis. As part of the study, 2 patients are vaccinated against poliomyelitis. One patient receives an intramuscular inactivated vaccine and the other patient receives a live attenuated oral vaccine. One month after vaccination, the levels of which of the following poliovirus antibodies will differ the most between these 2 patients?

A. Cerebrospinal fluid IgG

B. Duodenal luminal IgA

C. Serum IgA

D. Serum IgG

E. Serum IgM

Submit

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- A. Cerebrospinal fluid IgG (3%)
- ✓ B. Duodenal luminal IgA (49%)
- C. Serum IgA (12%)
- D. Serum IgG (27%)
- E. Serum IgM (7%)

Omitted
Correct answer
B

49%
Answered correctly

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Explanation

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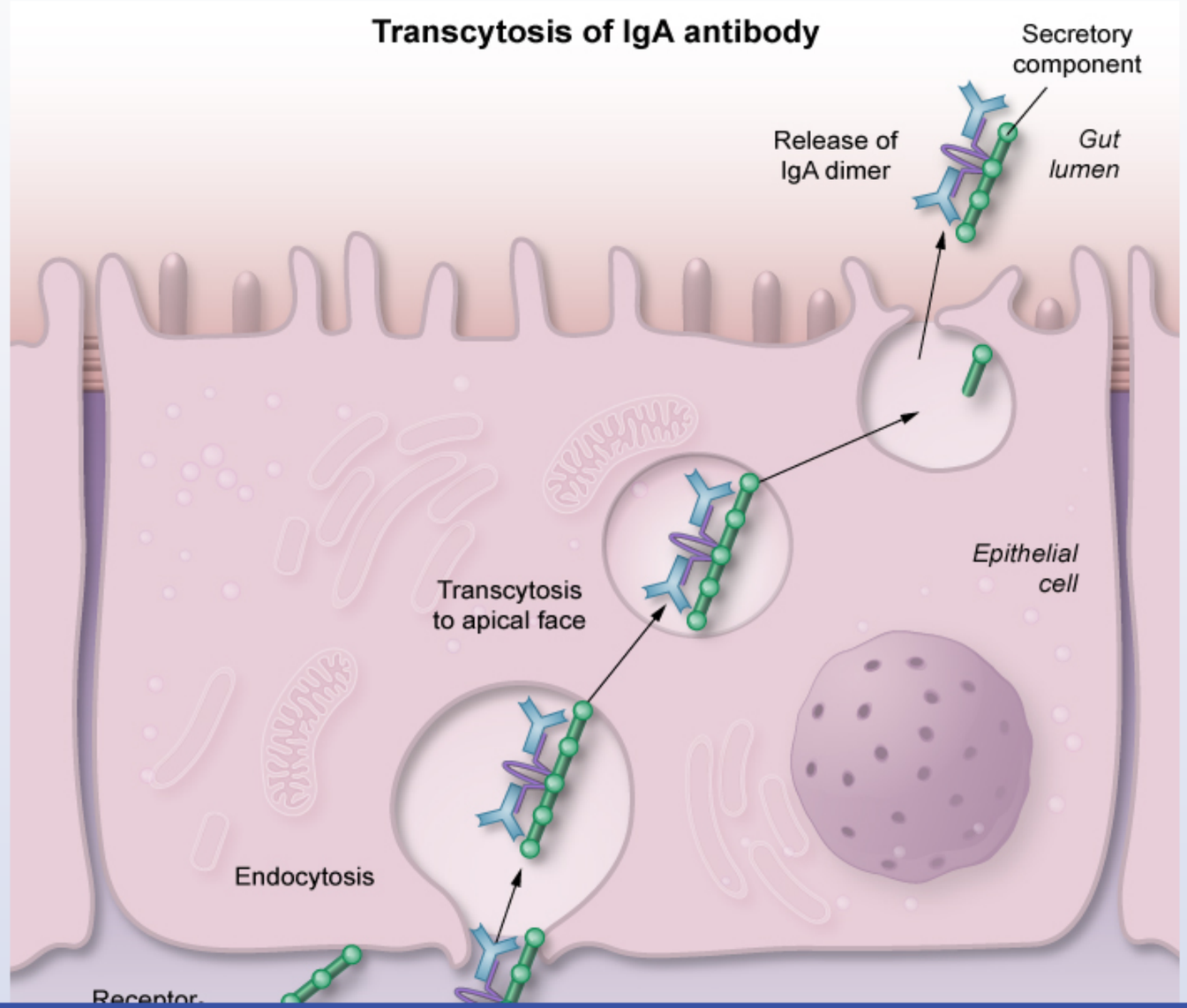

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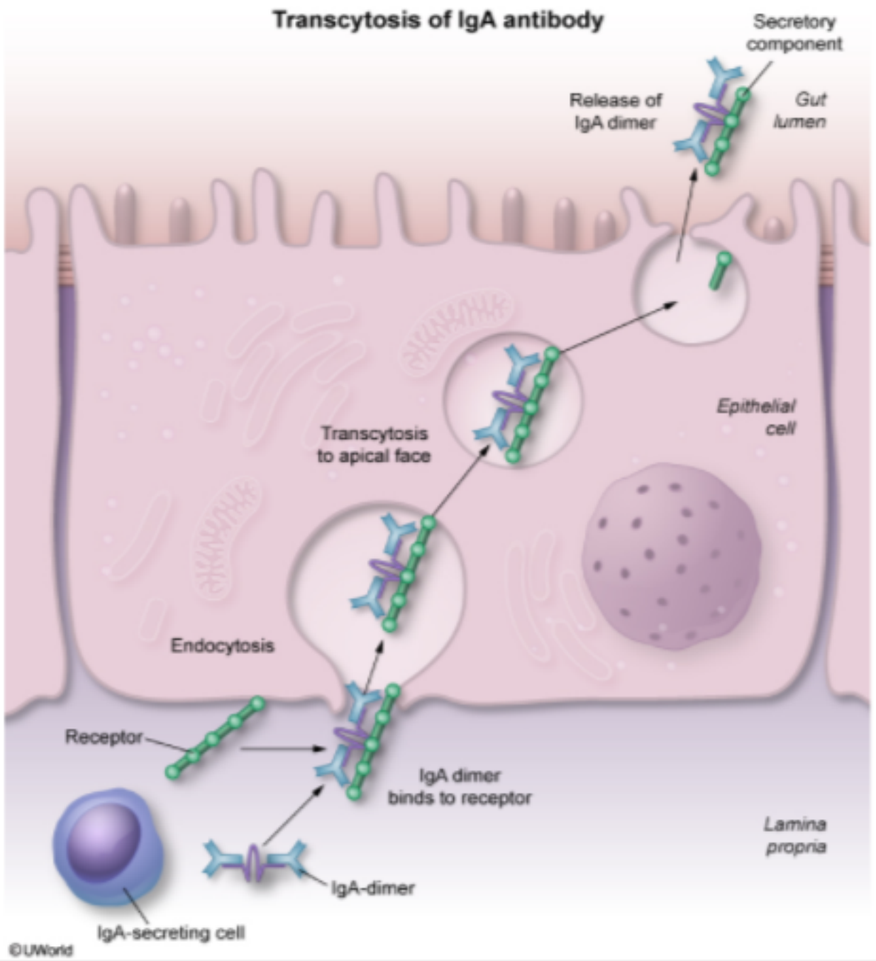

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IgA-secreting cell

Secretory IgA is the major antibody associated with **mucosal immunity**. Upon intestinal exposure to a novel antigen, B cells found in mesenteric lymph nodes and Peyer's patches become activated and preferentially migrate to the lamina propria underlying the intestinal mucosa. There, they become fully differentiated plasma cells that begin to synthesize IgA dimers (linked by **J chain**). These IgA dimers then bind to the polymeric immunoglobulin receptor (pIgR) found on the basolateral surface of intestinal epithelial cells and undergo transcytosis. As the linked IgA dimer is released into the intestinal lumen, a portion of pIgR remains attached to the antibody (**secretory component**), forming the complete secretory IgA molecule.

Stimulation of local secretory IgA production is best promoted when the corresponding mucosal surfaces are **directly stimulated** by the antigen. In addition, live attenuated vaccines generally produce stronger immune responses than killed vaccines by acting as a persistent stimulus that better activates helper and cytotoxic T cells. As a result, the **live attenuated oral** (Sabin) poliovirus vaccine generates a much more robust oropharyngeal and intestinal mucosal IgA response than the inactivated poliovirus (Salk) vaccine.

(Choice A) Cerebrospinal fluid IgG antibody levels can increase due to a rise in local production (eg, multiple sclerosis, viral CNS infections) or inflammation of the blood-brain barrier (eg, trauma, meningitis), leading to excessive leakage of plasma proteins.

(Choices C, D, and E) Serum IgA (mainly monomeric), IgG, and IgM increase with both forms of the polio vaccine and are protective against viral dissemination. Serum IgG and IgM can also be secreted by the mucosa although to a lesser extent than secretory IgA (explaining why most patients with selective IgA deficiency are asymptomatic).

Educational objective:
The live attenuated oral (Sabin) poliovirus vaccine produces a stronger mucosal secretory IgA immune response than does the inactivated poliovirus (Salk) vaccine. This increase in mucosal IgA offers immune protection at the site of viral entry by inhibiting attachment to intestinal epithelial cells.

Immunology	General Principles	Immunoglobulins
Subject	System	Topic

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A 5-year-old boy with severe, recurrent respiratory infections is undergoing evaluation. Sputum studies reveal intracellular bacteria. Further testing shows that the patient's T cells lack the IL-12 receptor. Supplementation with which of the following substances would most likely improve this patient's condition?

A. Early complement components
B. GM-CSF
C. Immunoglobulins
D. Interferon-gamma
E. Interleukin-4

Submit

A 5-year-old boy with severe, recurrent respiratory infections is undergoing evaluation. Sputum studies reveal intracellular bacteria. Further testing shows that the patient's T cells lack the IL-12 receptor. Supplementation with which of the following substances would most likely improve this patient's condition?

- A. Early complement components (2%)
- B. GM-CSF (5%)
- C. Immunoglobulins (7%)
- ✓ D. Interferon-gamma (78%)
- E. Interleukin-4 (5%)

Omitted
Correct answer
D

78%
Answered correctly

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Time Spent

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Last Updated

Explanation

T cell subsets		
	TH1	TH2
Immunity	Cell-mediated	Humoral (antibody-mediated)
Function	Activate macrophages & $CD8^+$ T cells	Activate B cells, promote class-switching

T cell subsets		
	TH1	**TH2**
Immunity	Cell-mediated	Humoral (antibody-mediated)
Function	Activate macrophages & $CD8^+$ T cells	Activate B cells, promote class-switching
Cytokines	IL-2, IFN-γ, lymphotoxin β	IL-4, 5, 10, & 13
Result	Cytotoxicity; delayed hypersensitivity	Secretion of antibodies

IFN = interferon.

Helper T cells that have not yet contacted antigens are called **naive (Th0) cells** and have T-cell receptors (TCRs) and CD4 proteins on their surface. An **antigen-MHC class II complex** on an antigen-presenting cell (eg, macrophage, dendritic cell) can activate a naive Th cell by interacting with both TCR and CD4. The activated T cell then differentiates into either a Th1 or Th2 cell.

If the antigen is presented by a macrophage, the macrophage will produce **IL-12**, which stimulates differentiation into **Th1** cells. A deficiency of IL-12 receptors on naive T cells prevents differentiation into Th1 cells, which produce interferon-gamma (**IFN-γ**). IFN-γ is responsible for activation of the macrophage and $CD8^+$ cytotoxic response against intracellular organisms, such as **mycobacteria**. Therefore, individuals with an IL-12 receptor deficiency are susceptible to severe, persistent mycobacterial infections. Administration of IFN-γ improves the immune response to mycobacterium in these patients.

(Choices A and B) Both complement and GM-CSF (granulocyte-macrophage colony-stimulating factor) play a part in the immune response against pathogens such as mycobacterium. However, patients with an IL-12 receptor deficiency are unable to produce sufficient IFN-γ and therefore would not be able to mount a sufficient immune response to mycobacterium without IFN-γ supplementation.

(Choices C and E) Formation of Th2 cells is induced by IL-4, which also plays a role in B cell differentiation and the production of immunoglobulins. Administration of immunoglobulins or IL-4 would improve the immune response against extracellular bacteria or viruses but

Result	Cytotoxicity, delayed hypersensitivity	Secretion of antibodies

IFN = interferon.

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(Choices C and E) Formation of Th2 cells is induced by IL-4, which also plays a role in B cell differentiation and the production of immunoglobulins. Administration of immunoglobulins or IL-4 would improve the immune response against extracellular bacteria or viruses but would not be effective in stimulating an immune response against intracellular bacteria such as mycobacterium.

Educational objective:
IL-12 stimulates the differentiation of naive Th0 cells into Th1 cells. Patients with IL-12 receptor deficiency are susceptible to severe mycobacterial infections due to the inability to mount a strong cell-mediated granulomatous immune response; therefore, they require treatment with IFN-γ.

Immunology	Allergy & Immunology	Cell mediated immunity
Subject	System	Topic

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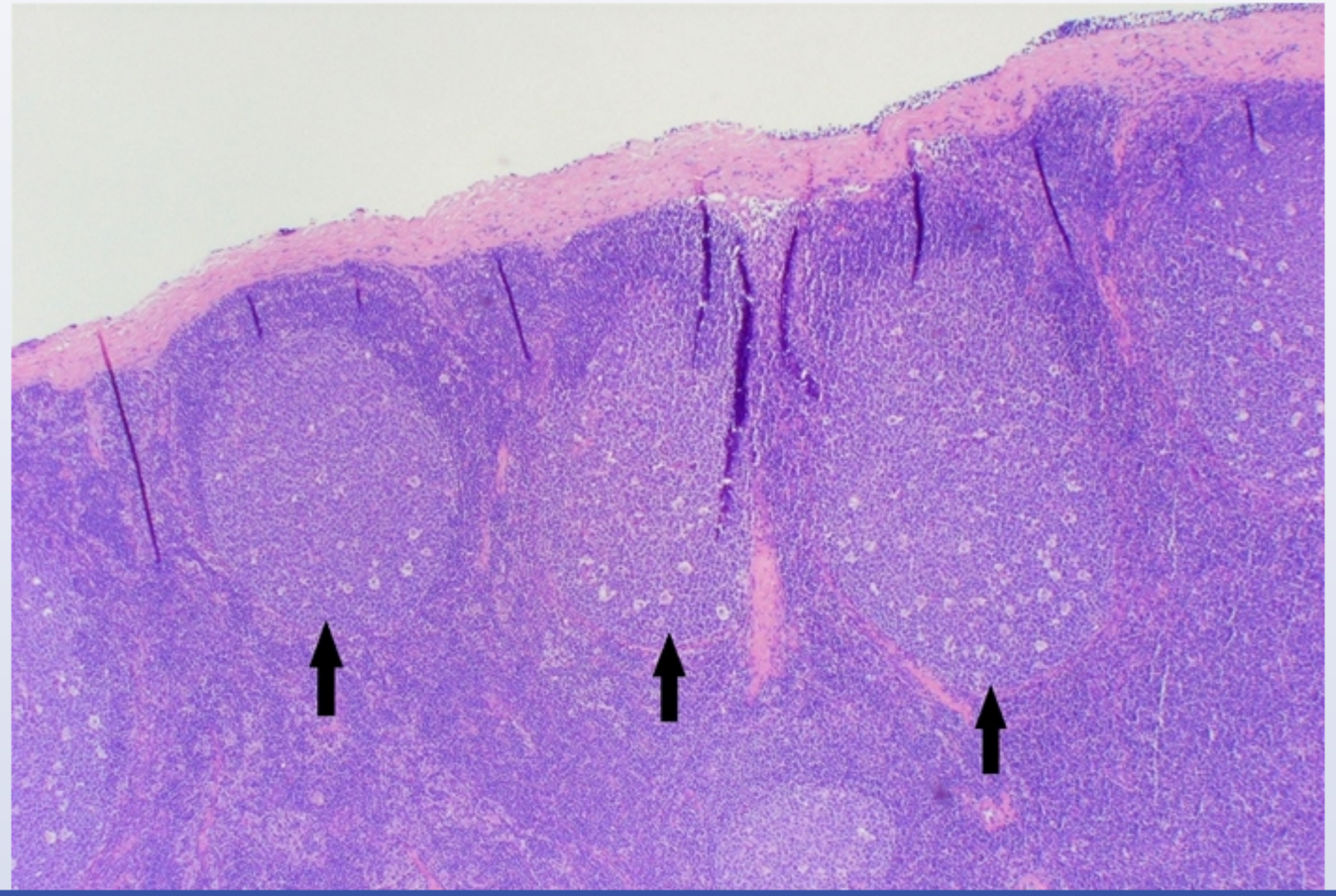
An 8-year-old boy is brought to the pediatrician with fever, runny nose, and malaise. After examining the child, the pediatrician determines that he has a viral infection and does not require any specific treatment. The mother asks why an antibiotic is not necessary, and the physician explains the differences between bacterial and viral infections. The immune system is composed of both cellular and humoral components, which are able to mount an effective response against many types of viral and bacterial infections. A section of a normal lymph node is shown in the image below.



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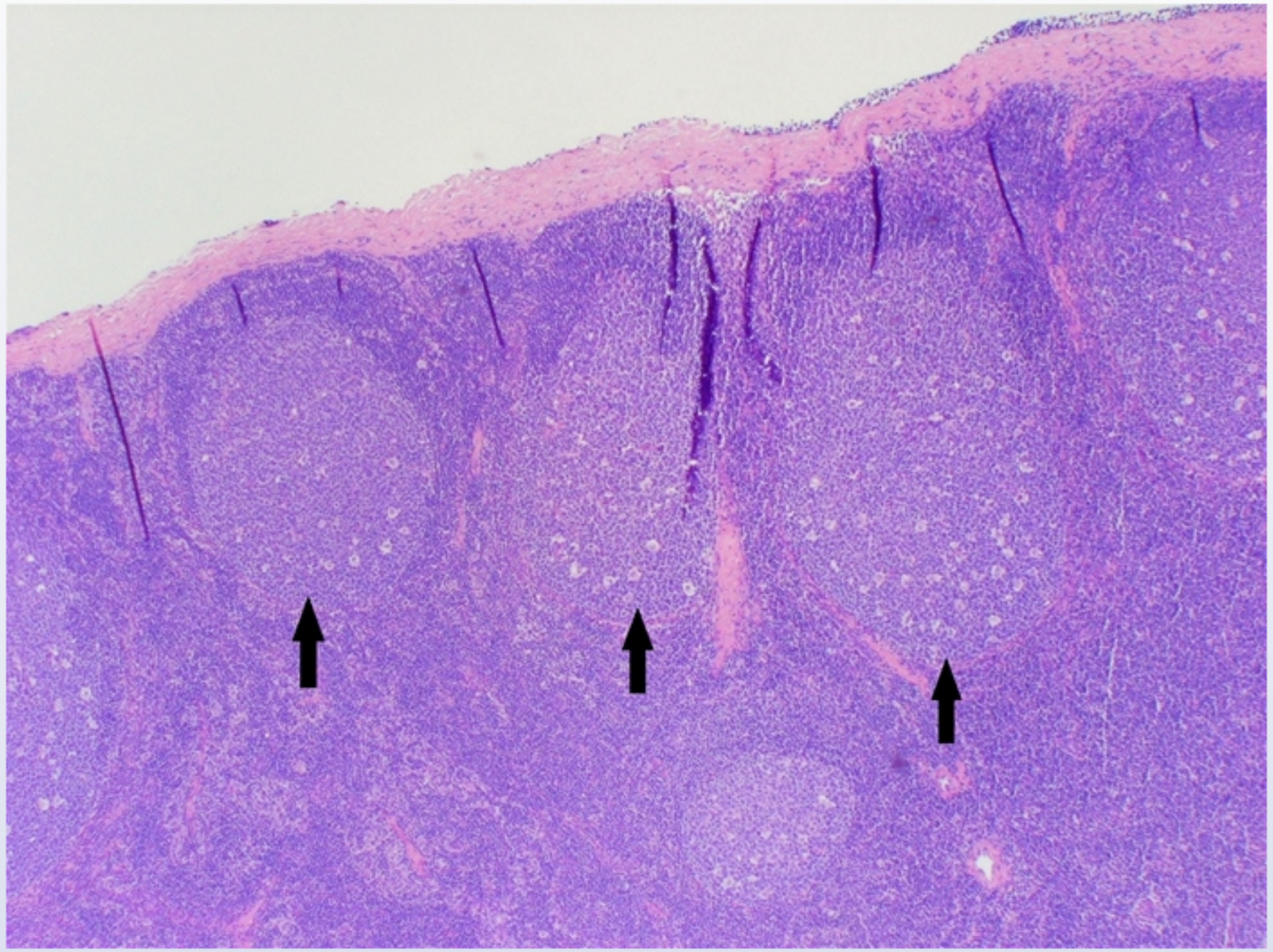

The structures indicated by the arrows are most likely to contain cells undergoing which of the following processes?

A. Isotype switching

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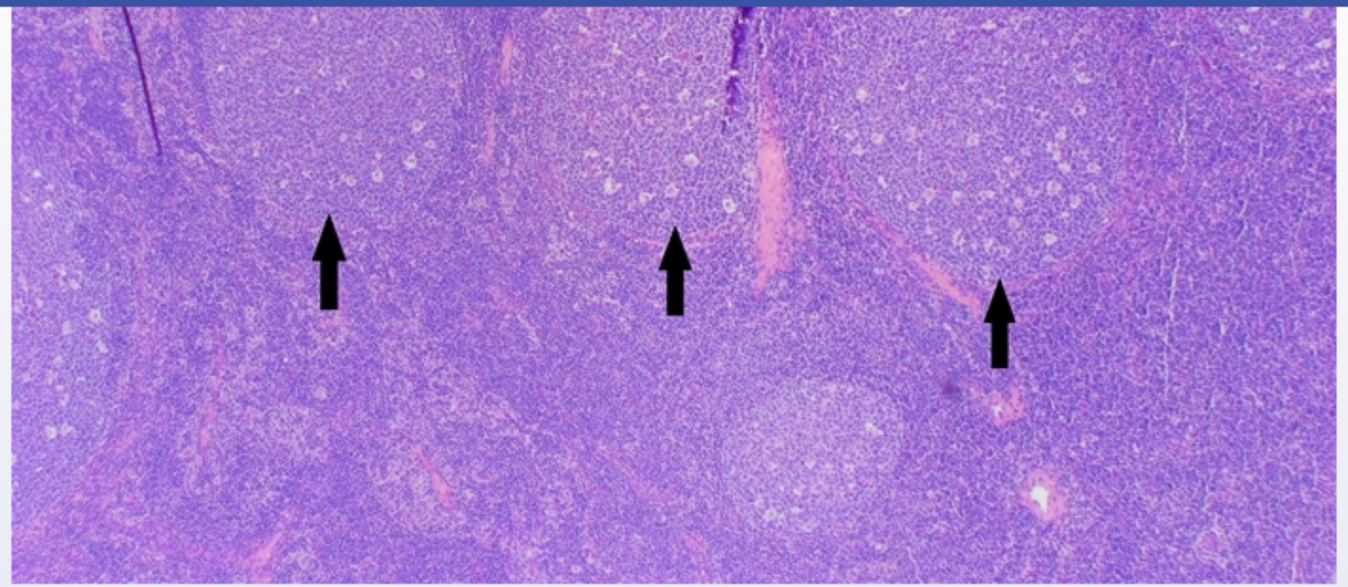

The structures indicated by the arrows are most likely to contain cells undergoing which of the following processes?

- A. Isotype switching
- B. Negative selection
- C. Tolerance development
- D. VDJ recombination
- E. VJ recombination

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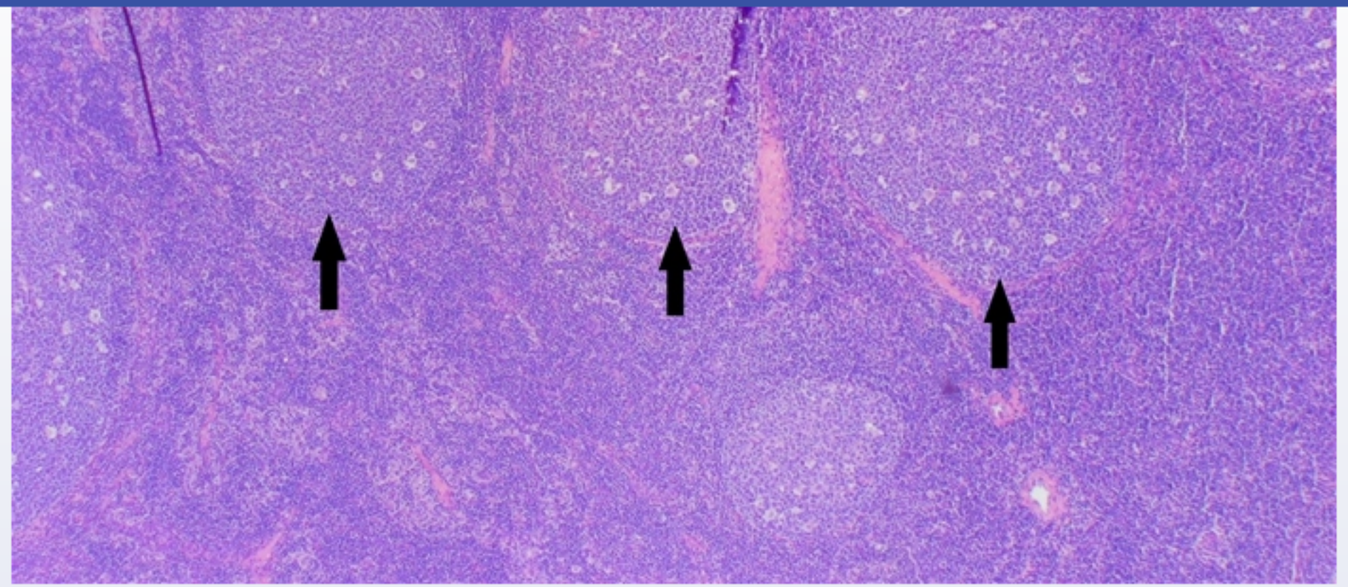

The structures indicated by the arrows are most likely to contain cells undergoing which of the following processes?

- ✓ A. Isotype switching (61%)
- B. Negative selection (14%)
- C. Tolerance development (4%)
- D. VDJ recombination (17%)
- E. VJ recombination (2%)

Omitted
Correct answer

61%
Answered correctly

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04/23/2020
Last Updated

Explanation

B-cell precursors proliferate and mature in the bone marrow. Mature B-cells then leave the bone marrow and migrate to lymphoid organs and peripheral tissues, where they are exposed to antigens. On first exposure to a new antigen, a clone of B-cells becomes activated. Some activated B-cells differentiate into short-lived plasma cells that release antigen-specific IgM through a T-cell independent process. However, most activated B-cells migrate to lymphoid follicles located in the lymph node cortex where they form germinal centers (arrows) that are the site of B-cell proliferation during the immune response. A portion of these activated B-cells form long-lived memory cells that remain dormant in the lymph node until the next encounter with the same antigen, but the majority transform into antibody-secreting plasma cells.

Isotype switching (from IgM to other types of immunoglobulins) also occurs in the germinal centers late in the primary response, providing activated B-cells the ability to produce antigen-specific antibodies of differing isotypes. Heavy chain constant regions are isotype-specific and distinguish the 5 isotypes (IgM, IgG, IgA, IgE, and IgD), while the variable regions are antigen-specific. Light chains are antigen-specific and do not determine isotype. Isotype switching first requires interaction of the CD40 receptor on activated B-cells with the CD40 ligand (CD154) expressed by activated T-cells. Afterward, isotype switching can occur through genetic rearrangement of the heavy chain constant regions. This process is modulated by T-cell cytokines such as IL-2, IL-4, IL-5, IL-6, and IFN-γ. After the primary immune response, subsequent encounters with the same antigen generate a predominantly IgG response (or IgA in the case of a mucosal response).

(Choice B) Negative selection refers to the deletion of T-cell clones that strongly bind to self-MHC antigens. This process occurs in the fetal thymus and contributes to the development of tolerance to one's own antigens.

(Choice C) Tolerance is immunologic unresponsiveness to self antigens. Central tolerance is acquired within the fetal thymus during negative selection. Peripheral tolerance develops by means of T-cell anergy, which is the functional inactivation of T-cells that are reactive to self antigens.

(Choices D and E) Recombination of the V, D, and J regions of heavy chains and the V and J regions of light chains occurs via DNA rearrangement. After undergoing immunoglobulin gene rearrangement, each B-cell makes antibodies of a single specificity. An enormous variety of different immunoglobulin molecules can potentially be produced through rearrangement. Recombination of these regions occurs during B-cell maturation within the bone marrow. Later on, during the primary immune response, affinity maturation occurs in the germinal centers through the process of somatic hypermutation.

Educational objective:

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A 35-year-old woman comes to the office due to fever, headache, severe muscle aches, and sore throat for the last 4 days. Physical examination shows mild pharyngeal erythema and nasal congestion. A rapid influenza antigen test is positive. The patient's condition improves over the next several days despite receiving only symptomatic treatment. In response to the influenza virus, infected respiratory epithelial cells begin secreting increased quantities of interferons. The specific interferons secreted by these cells will most likely cause which of the following changes?

A. Decreased apoptosis of infected cells

B. Decreased protein synthesis by infected cells

C. Increased class II MHC expression

D. Increased intracellular killing by macrophages

E. Increased neutrophil recruitment

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- A. Decreased apoptosis of infected cells (1%)
- ✓ B. Decreased protein synthesis by infected cells (36%)
- C. Increased class II MHC expression (15%)
- D. Increased intracellular killing by macrophages (38%)
- E. Increased neutrophil recruitment (7%)

Omitted
Correct answer
B

36%
Answered correctly

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Explanation

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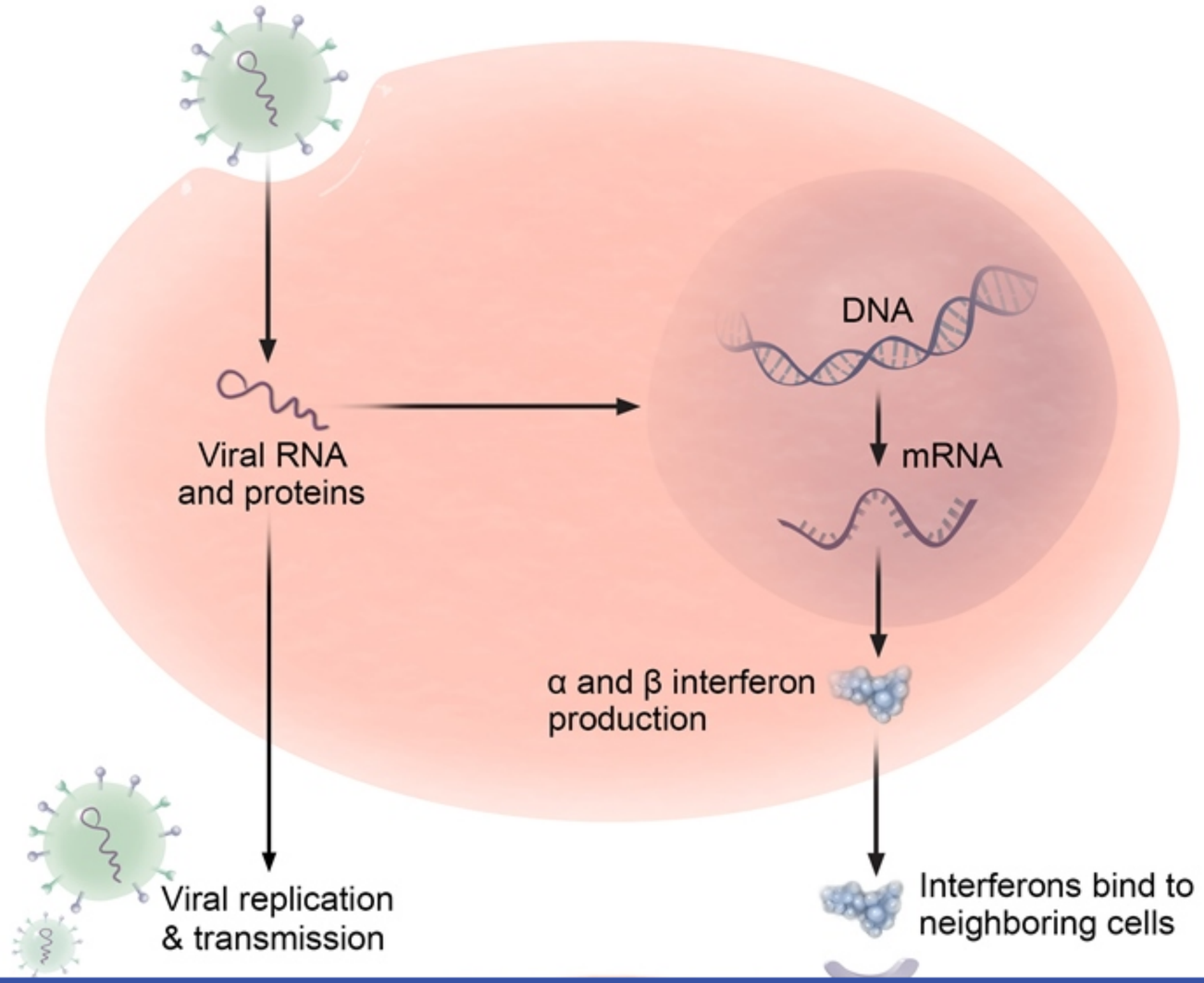
Antiviral actions of α and β interferon



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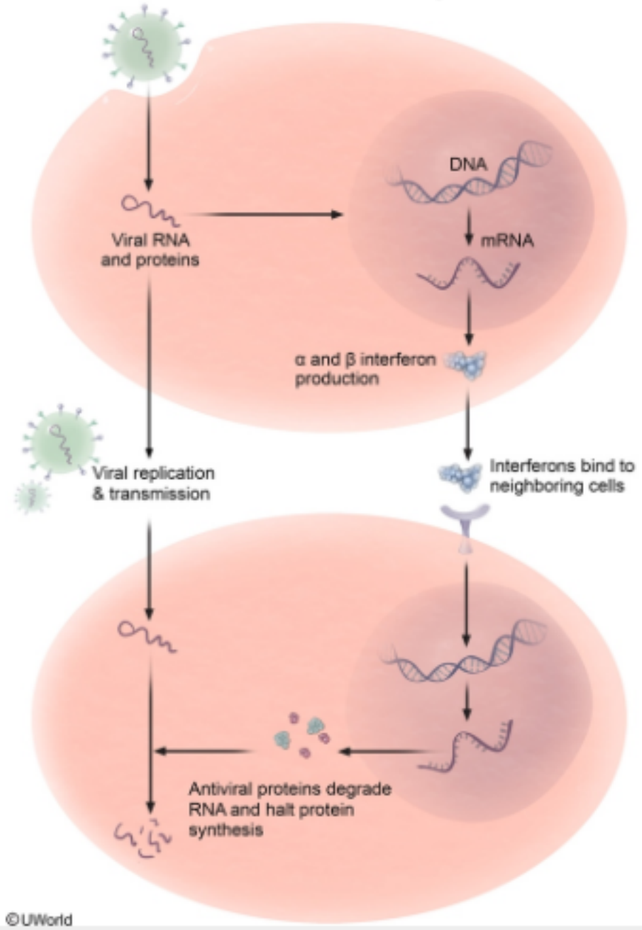
Antiviral actions of α and β interferon



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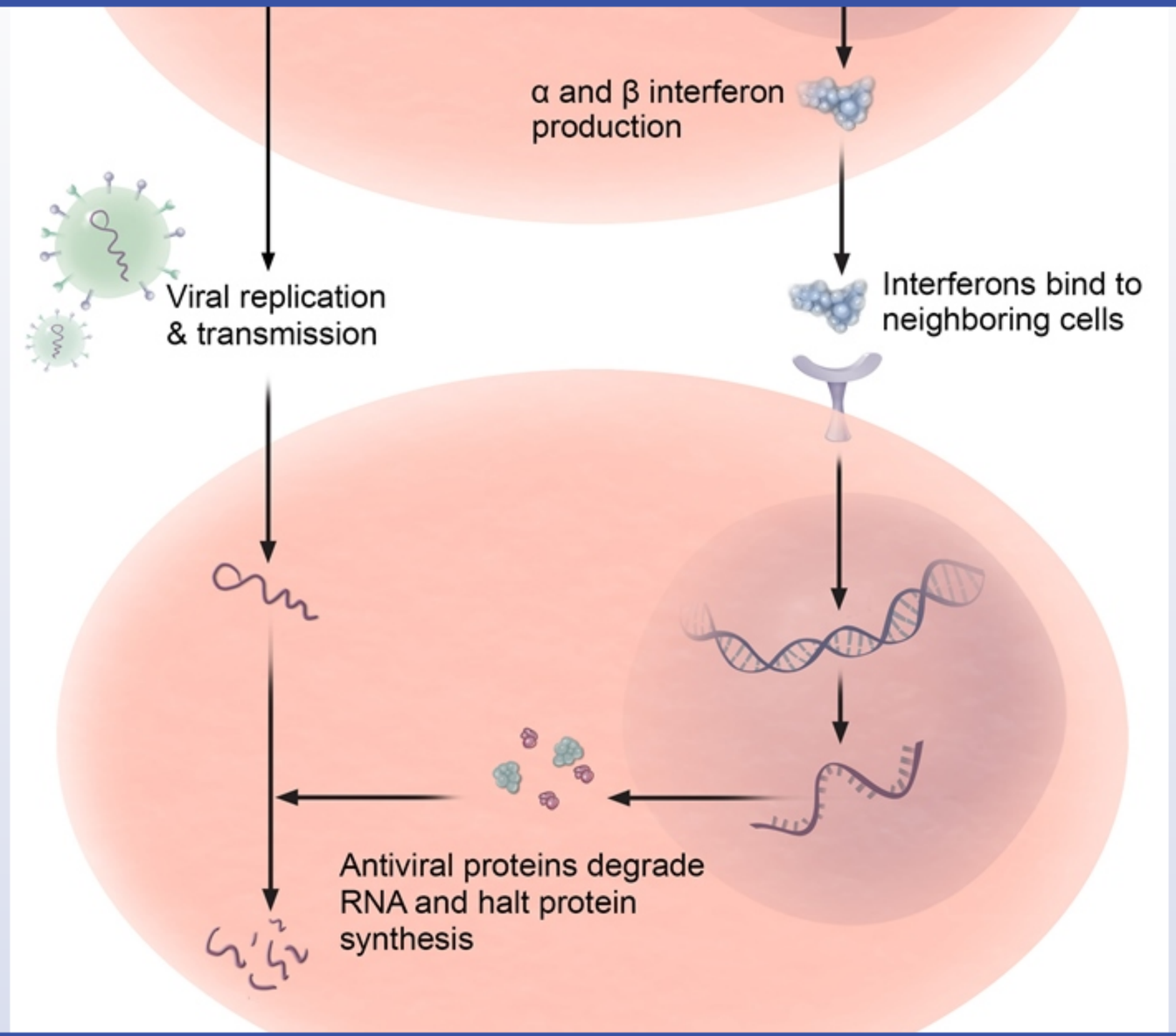

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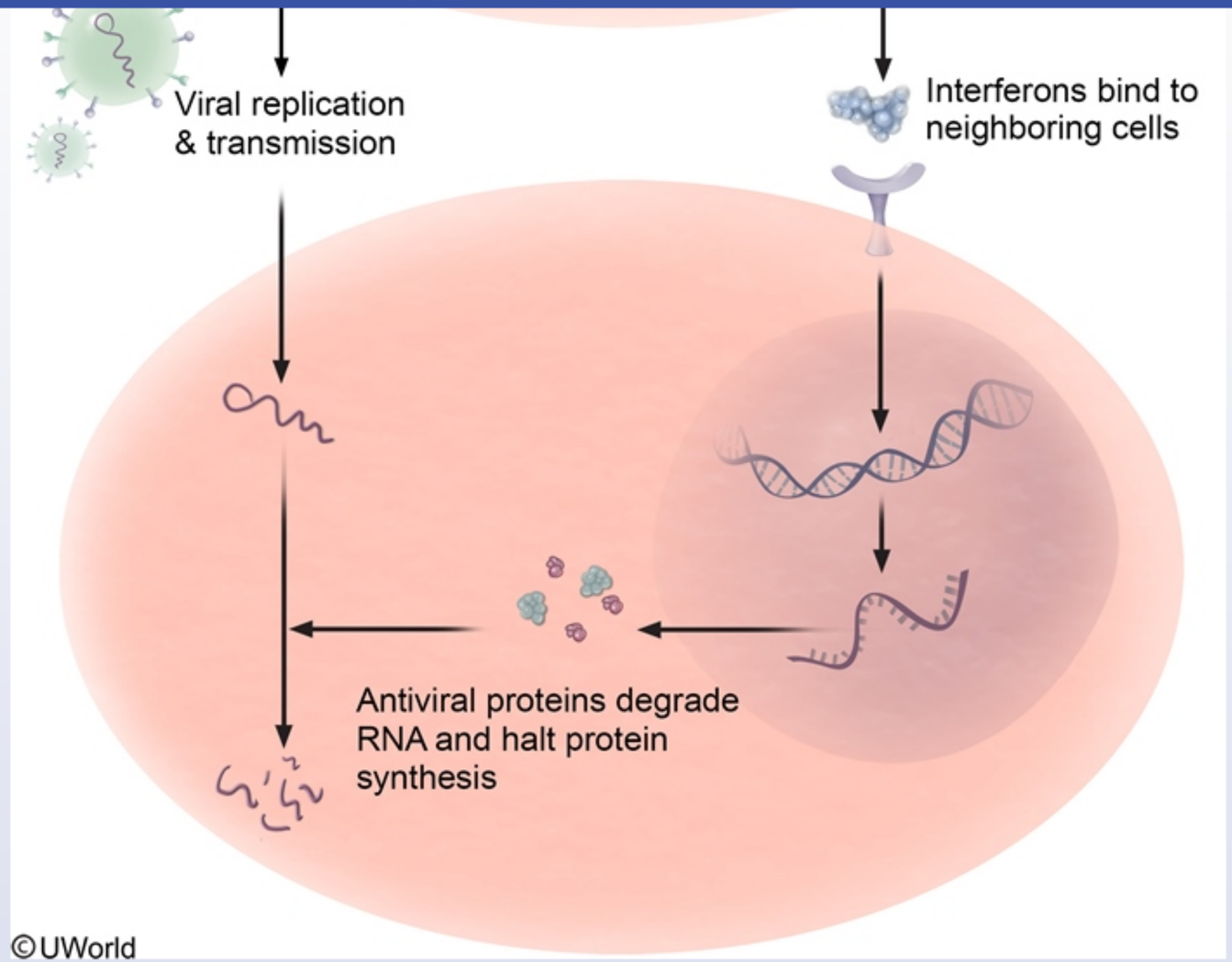

Type I interferons (α and β) are synthesized by most human cells in response to **viral infections**. Once secreted, α and β interferons bind to type I interferon receptors found on infected and neighboring cells (autocrine/paracrine signaling). This results in transcription of antiviral enzymes capable of **halting protein synthesis**, such as RNase L (endonuclease that degrades all RNA in the cell) and protein kinase R (inactivates eIF-2

Type I interferons (α and β) are synthesized by most human cells in response to **viral infections**. Once secreted, α and β interferons bind to type I interferon receptors found on infected and neighboring cells (autocrine/paracrine signaling). This results in transcription of antiviral enzymes capable of **halting protein synthesis**, such as RNase L (endonuclease that degrades all RNA in the cell) and protein kinase R (inactivates eIF-2, inhibiting translation initiation). However, these enzymes become active **only** in the presence of **double-stranded RNA**, which forms in infected cells as a result of viral replication. As a result, normal metabolism and protein synthesis can continue in uninfected cells but is **selectively** inhibited in virally infected cells.

(Choice A) Interferons α and β induce MHC class I expression on all cells and stimulate the activity of natural killer (NK) and cytotoxic T cells. These processes act to increase the proportion of virally infected cells that undergo apoptosis.

(Choices C and D) Interferon γ is a type II interferon produced mainly by T cells and NK cells. It promotes T_H1 differentiation, increases expression of class II MHC molecules on antigen-presenting cells, and improves the intracellular killing ability of macrophages. However, virally infected respiratory epithelial cells would secrete interferons α and β, not interferon γ.

(Choice E) Neutrophils primarily phagocytize and destroy bacterial and fungal pathogens. They do not play a significant role in fighting viral infections, and α and β interferon release by virally infected cells does not promote neutrophil recruitment.

Educational objective:
Interferons α and β are produced by most human cells in response to viral infections. The production of α and β interferons helps suppress viral replication by halting protein synthesis and promoting apoptosis of infected cells, limiting the ability of viruses to spread through the tissues.

References

- Immunomodulatory functions of type I interferons.
- Interferons and viruses: an interplay between induction, signalling, antiviral responses and virus countermeasures.

Immunology	General Principles	Cytokines
Subject	System	Topic

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A 3-month-old girl is brought to the emergency department due to fever, irritability, and vomiting for the past 2 days. On examination, she is ill-looking, lethargic, and febrile. Blood cultures grow *Mycobacterium tuberculosis*. One of her brothers died from disseminated mycobacterial infection during infancy. Impairment of which of the following protective mechanisms is most likely contributing to this patient's infection?

- A. Antibody production
- B. Complement production
- C. Interferon signaling
- D. Isotype switching
- E. Leukocyte adhesion

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- A. Antibody production (4%)
- B. Complement production (8%)
- ✓ C. Interferon signaling (75%)
- D. Isotype switching (3%)
- E. Leukocyte adhesion (7%)

Omitted
Correct answer
C

75%
Answered correctly

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04/12/2020
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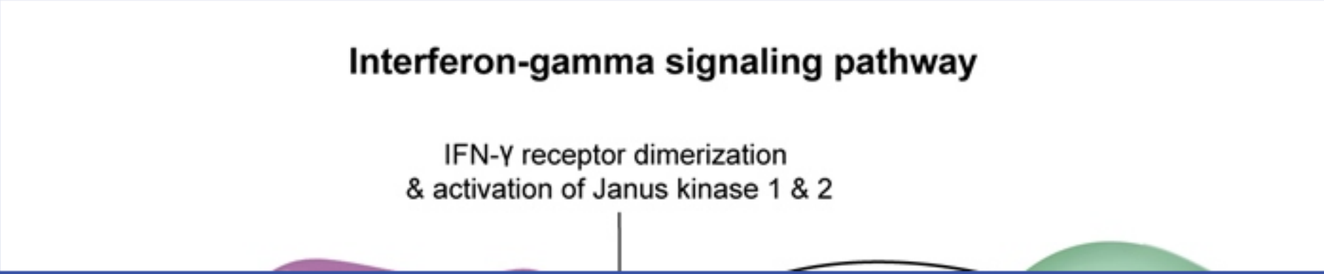
Explanation



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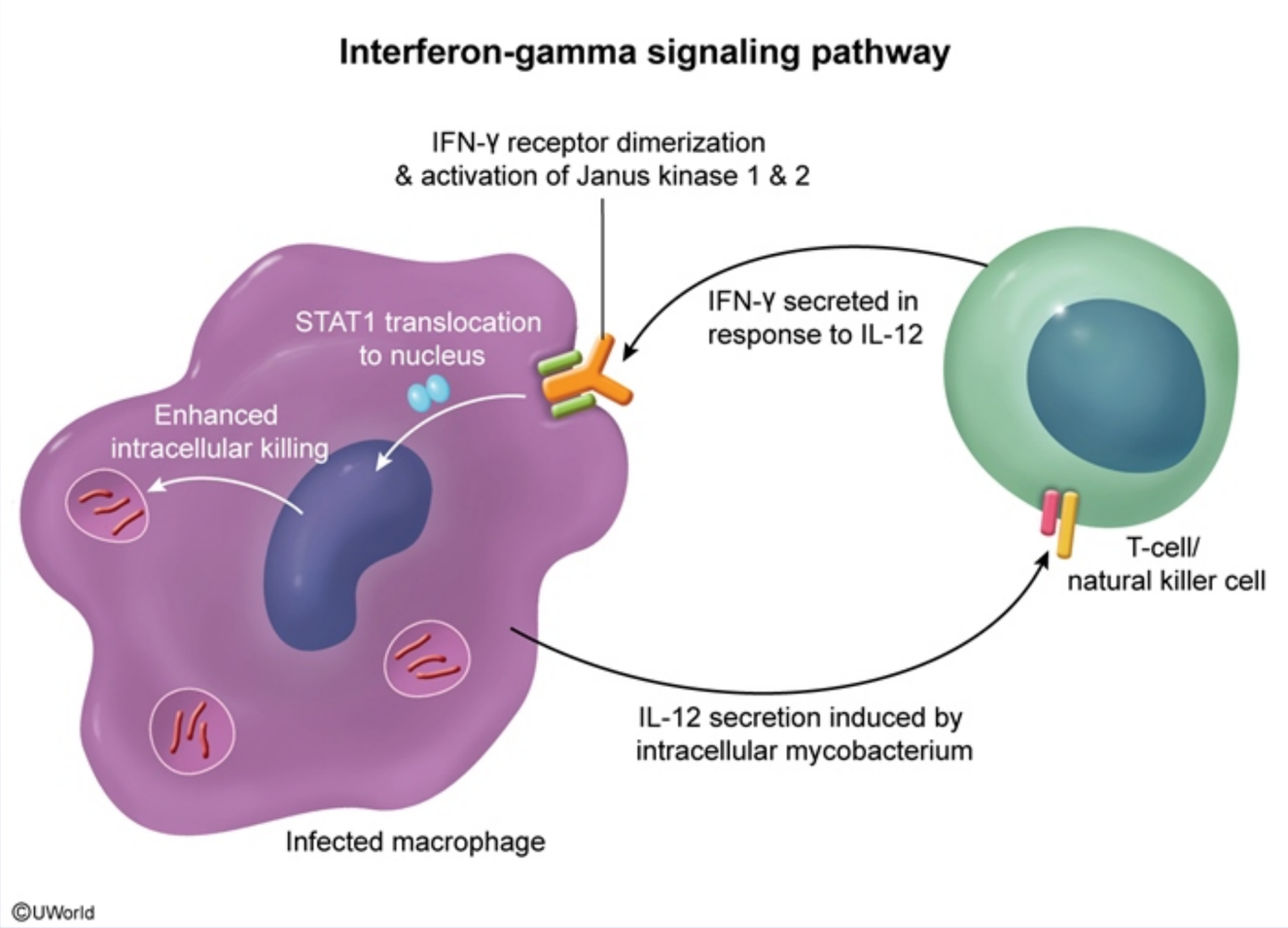

Host defense against **mycobacterial infections** depends on the ability of **macrophages** to sequester mycobacteria in granulomas and directly kill the bacteria in phagosomes. Infected macrophages produce **IL-12**, which stimulates T cells and natural killer cells to produce **interferon-γ** (IFN-γ). Binding of IFN-γ to its receptor on a macrophage causes transcription of IFN-γ-regulated genes through activation of the JAK-STAT signaling pathway. The result is upregulation of IL-12 production, enhanced mycobacterial intracellular killing in phagolysosomes, and production of tumor necrosis factor-α (TNF-α) which promotes formation of granulomas.

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Autosomal recessive deficiencies of the IFN-γ receptor (or other elements of this pathway) result in **disseminated mycobacterial disease** (or BCG infection if the vaccine is administered) in infancy or early childhood. These patients require lifelong treatment with continuous antimycobacterial antibiotics.

(Choice A) X-linked agammaglobulinemia (XLA) is an immunodeficiency disorder characterized by significantly reduced mature B cell production. These patients are deficient in all types of immunoglobulins; predisposing them to recurrent lower respiratory tract infections due to encapsulated bacteria (eg, *S. pneumoniae*, *H. influenzae*).

(Choice B) Deficiencies of C5-C9, the components of the complement membrane attack complex, can lead to recurrent infections with *Neisseria meningitidis* or *gonorrhoeae*.

(Choice D) Isotype switching is a process that occurs in naïve B lymphocytes on initial exposure to antigen. It is dependent on the interaction of CD40 with its ligand and cytokines including IL-4 and IL-5, which promote IgE and IgA class switching, respectively.

(Choice E) Leukocyte adhesion deficiency is a rare immunodeficiency resulting from a defect in CD18, an integrin component that allows for leukocyte adherence and transmigration through endothelial walls. These patients present with delayed separation of the umbilical cord, poor wound healing, and recurrent cutaneous infections without pus formation.

Educational objective:
Inherited defects involving the interferon-γ signaling pathway result in disseminated mycobacterial disease in infancy or early childhood. Patients require lifelong treatment with antimycobacterial agents.

References

- Impaired interferon gamma-mediated immunity and susceptibility to mycobacterial infection in childhood.

A scientist is interested in the mechanisms by which leukocytes traffic to sites of inflammation and infection. She finds that endothelial cells increase the expression of certain cell surface molecules in response to cytokines to allow for leukocyte trafficking. She subsequently creates a knockout mouse that has a deletion in the platelet endothelial cell adhesion molecule 1 (PECAM-1) gene. The protein product of this gene is mainly localized to specific areas on the endothelial cells. Absent expression of this gene will most likely affect which of the following neutrophil functions?

A. Crawling
B. Margination
C. Rolling
D. Tight adhesion
E. Transmigration

Submit

A scientist is interested in the mechanisms by which leukocytes traffic to sites of inflammation and infection. She finds that endothelial cells increase the expression of certain cell surface molecules in response to cytokines to allow for leukocyte trafficking. She subsequently creates a knockout mouse that has a deletion in the platelet endothelial cell adhesion molecule 1 (PECAM-1) gene. The protein product of this gene is mainly localized to specific areas on the endothelial cells. Absent expression of this gene will most likely affect which of the following neutrophil functions?

- A. Crawling (1%)
- B. Margination (12%)
- C. Rolling (23%)
- D. Tight adhesion (31%)
- ✓ E. Transmigration (31%)

Omitted
Correct answer
E

31%
Answered correctly

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Last Updated

Explanation

Inflammation is an important process in the defense against various pathogens. It is characterized by the passage of leukocytes into the inflamed tissue. The following steps are involved in inflammatory leukocyte accumulation:

1. Margination: Increased vascular leakage in the microvasculature leads to hemoconcentration and decreased wall shear stress, improving the contact of neutrophils with the endothelial lining **(Choice B)**.

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Inflammation is an important process in the defense against various pathogens. It is characterized by the passage of leukocytes into the inflamed tissue. The following steps are involved in inflammatory leukocyte accumulation:

1. Margination: Increased vascular leakage in the microvasculature leads to hemoconcentration and decreased wall shear stress, improving the contact of neutrophils with the endothelial lining **(Choice B)**.

2. Rolling: Neutrophils roll on the endothelium via the loose binding of sialylated carbohydrate groups, such as Sialyl Lewis X or PSGL-1, to **L-selectin** on neutrophils or **E-selectin/P-selectin** on endothelial cells **(Choice C)**. Cytokine stimulation greatly increases expression of endothelial selectins.

3. Activation: Slow rolling allows the leukocytes to sample the chemokines secreted by the inflamed tissue. This activates integrins by inducing a signaling cascade that results in a conformational change in the integrins necessary for binding.

4. Tight adhesion and crawling: Neutrophils become firmly attached to the endothelium via the binding of **CD 18 beta 2 integrins** (**Mac-1** and **LFA-1**) to **intercellular adhesion molecule-1** (**ICAM-1**) on endothelial cells (**Choices A and D**).

5. Transmigration: After crawling to the endothelial cell periphery, neutrophils eventually migrate out of the vasculature by squeezing in between the cells via integrin attachments and adherence to **platelet endothelial cell adhesion molecule 1** (**PECAM-1**). This protein is found primarily at the peripheral intercellular junctions of endothelial cells.

Three leukocyte adhesion deficiency (LAD) syndromes have been identified whereby leukocytes cannot leave the vasculature to migrate into tissues under conditions of inflammation. All are rare, autosomal recessive disorders.

LAD type 1 results from the absence of CD18. This leads to the inability to synthesize the beta-2 integrins Mac-1 and LFA1, affecting tight adhesion, crawling, and transmigration. The clinical manifestations include recurrent skin infections **without pus formation**, **delayed detachment of the umbilical cord**, and poor wound healing. LAD type 2 is a milder condition, with no delay in the separation of the umbilical cord and less severe and fewer infections. LAD type 3 is similar to type 1 and causes severe, recurrent bacterial infections, delayed separation of the umbilical cord, and bleeding complications (due to affected beta-3 integrins on platelets).

4. Tight adhesion and crawling: Neutrophils become firmly attached to the endothelium via the binding of **CD 18 beta 2 integrins** (**Mac-1** and **LFA-1**) to **intercellular adhesion molecule-1** (**ICAM-1**) on endothelial cells (**Choices A and D**).

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Educational objective:
Inflammation is characterized by the passage of circulating inflammatory leukocytes into the inflamed tissue. The steps involved include margination, rolling, activation, tight adhesion and crawling, and transmigration.

References

- Getting to the site of inflammation: the leukocyte adhesion cascade updated.
- Leukocyte adhesion deficiencies: molecular basis, clinical findings, and therapeutic options.

Immunology	General Principles	Inflammation
Subject	System	Topic

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4. Tight adhesion and crawling: Neutrophils become firmly attached to the endothelium via the binding of **CD 18 beta 2 integrins** (**Mac-1** and **LFA-1**) to **intercellular adhesion molecule-1** (**ICAM-1**) on endothelial cells (**Choices A and D**).

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Inflammation is characterized by the passage of circulating inflammatory leukocytes into the inflamed tissue. The steps involved include margination, rolling, activation, tight adhesion and crawling, and transmigration.

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Immunology	General Principles	Inflammation
Subject	System	Topic

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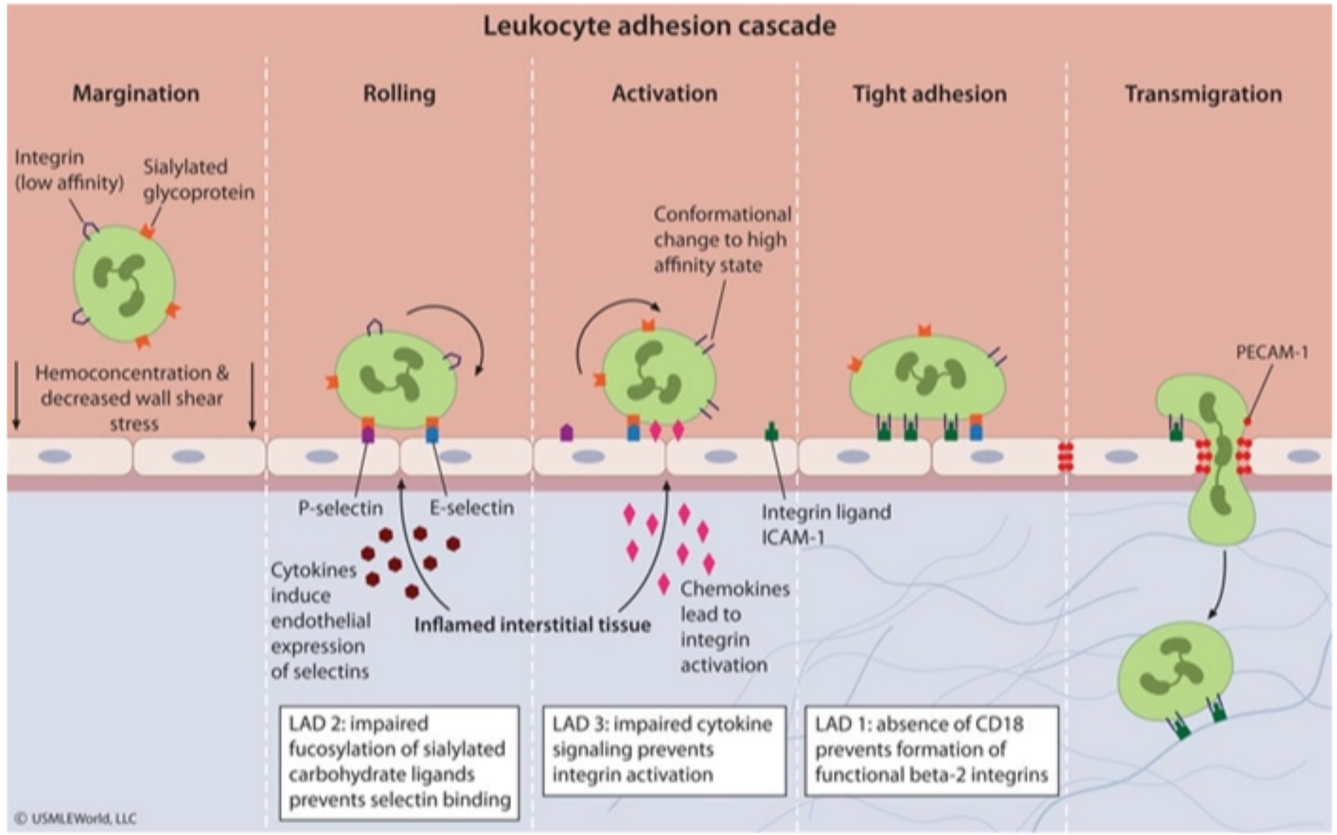

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Three leukocyte adhesion deficiency (LAD) syndromes have been identified whereby leukocytes cannot leave the vasculature to migrate into

An 18-month-old, partially vaccinated boy is brought to the office for a routine well-child examination. His parents have elected a delayed schedule for vaccine administration based on personal preferences. Today, the patient is scheduled to receive the *Haemophilus influenzae* serotype b (Hib) conjugate vaccine. The parents are given detailed information about the vaccine, but the mother asks, "Why is 'tetanus toxoid conjugate' listed on the package insert?" She adds that her son already received the diphtheria-tetanus-acellular pertussis (DTaP) vaccine. The parents request an explanation for the reason the Hib vaccine contains both the capsular polysaccharide of Hib as well as the conjugated tetanus toxoid. Which of the following best describes the purpose of Hib vaccine conjugation?

A. Decreases adverse vaccine reactions

B. Elicits T cell-dependent immune response

C. Eliminates the need for booster doses

D. Induces immunity against nontypeable *H influenzae*

E. Induces immunity against the conjugated toxoid

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- A. Decreases adverse vaccine reactions (1%)
- ✓ B. Elicits T cell-dependent immune response (74%)
- C. Eliminates the need for booster doses (9%)
- D. Induces immunity against nontypeable *H influenzae* (6%)
- E. Induces immunity against the conjugated toxoid (7%)

Omitted
Correct answer
B

74%
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02 secs
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01/21/2020
Last Updated

Explanation

Immunology	Polysaccharide vaccine	Polysaccharide-protein conjugate vaccine

Immunology	Polysaccharide vaccine	Polysaccharide-protein conjugate vaccine
Response type	B cell	B cell & T cell
Memory cell response	No	Yes
Relative duration of immunity	Short	Long
Immunogenicity in infancy	No	Yes

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***Haemophilus influenzae* serotype b (Hib)**, an encapsulated gram-negative coccobacillus, was previously a common, invasive, and potentially fatal cause of pneumonia, epiglottitis, and meningitis in children. Neonates are protected with maternal anti-Hib IgG antibodies from placental transfer in utero, but this protection wanes as the immunoglobulins are degraded during the first few months of life. Therefore, widespread vaccination with the Hib polysaccharide-protein conjugate vaccine series is recommended starting at age 2 months; this practice has dramatically reduced the incidence of Hib infection.

Bacteria with polysaccharide capsules (eg, Hib, *Streptococcus pneumoniae* [pneumococcus], *Neisseria meningitidis*) are antiphagocytic. The **polysaccharide capsule** provokes an **antibody-mediated (B cell) immune response** and is the primary antigenic constituent of vaccines against encapsulated bacteria. However, vaccines containing the polysaccharide antigen alone are ineffective in children age <2 years due to their immature humoral immunity. Therefore, the polysaccharide is **conjugated** with a **carrier protein** to amplify the patient's humoral response against the polysaccharide through T cell recruitment. The Hib conjugate vaccine contains a carrier protein that is derived from either a tetanus toxoid (TT) protein or an outer membrane protein (OMP) of *Neisseria meningitidis*. The polysaccharide-protein conjugate then becomes a T cell-dependent antigen. **Immunogenicity is increased** as a result of **T cell-dependent stimulation of B lymphocytes** and the **production of**

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(Choice A) Conjugation does not affect vaccine safety. The main adverse effects of the Hib vaccine include fever, irritability, and injection site reactions (eg, pain, redness, swelling).

(Choice C) Although conjugation allows for a more robust immune response, a 2- or 3-dose primary series in infancy followed by a booster dose is still required to achieve protective Hib antibody levels.

(Choice D) Nontypeable *H influenzae* represents nonencapsulated strains that generally cause local disease (eg, sinusitis, otitis media). These bacteria colonize the nasopharynx of most individuals age >5 years. The Hib vaccine does not confer protection against nontypeable *H influenzae*.

(Choice E) Conjugated OMP and TT protein do not elicit protective antibody levels. Therefore, a patient is not considered to be immunized against the pathogen that the carrier protein is derived from.

Educational objective:

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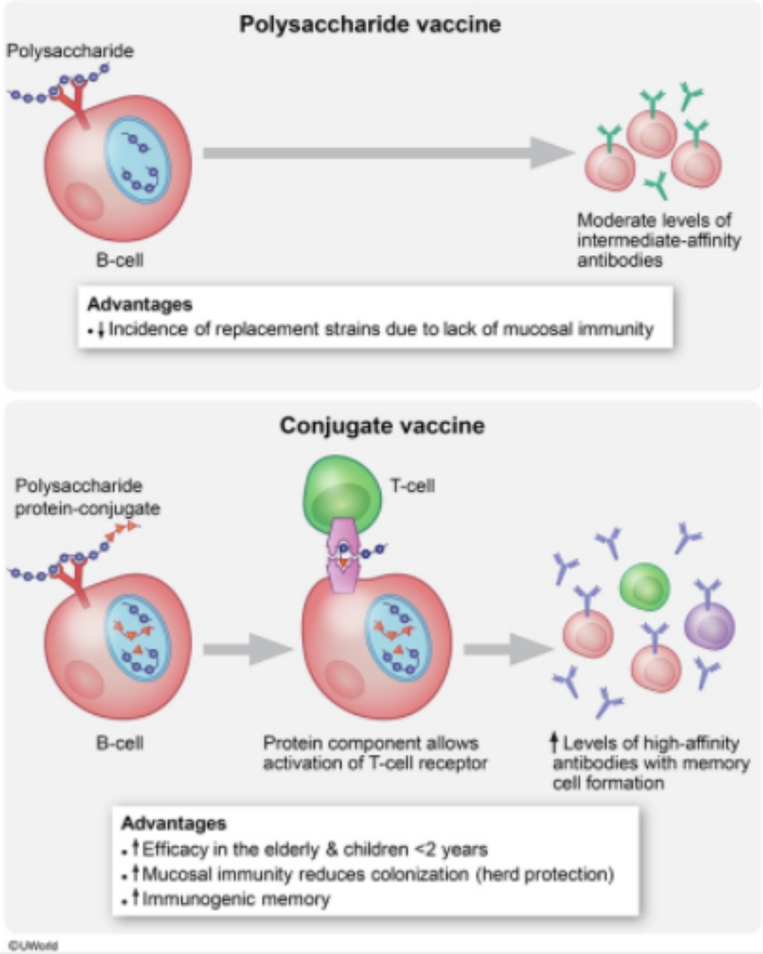
Exhibit Display



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Educational objective:

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(Choice E) Conjugated OMP and TT protein do not elicit protective antibody levels. Therefore, a patient is not considered to be immunized against the pathogen that the carrier protein is derived from.

Educational objective:
The *Haemophilus influenzae* serotype b vaccine consists of a capsular polysaccharide conjugated to a carrier protein (tetanus toxoid [TT] protein or outer membrane protein [OMP] of *Neisseria meningitidis*). Protein conjugation causes a T cell-mediated immune response leading to long-term immunity through production of memory B-lymphocytes.

References

- Long-term persistence of immunity and B-cell memory following Haemophilus influenzae type B conjugate vaccination in early childhood and response to booster.
- Optimising the use of conjugate vaccines to prevent disease caused by Haemophilus influenzae type b, Neisseria meningitidis and Streptococcus pneumoniae.

Immunology	Allergy & Immunology	Immunizations
Subject	System	Topic

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A 56-year-old woman with a history of heart failure is admitted to the hospital for orthotopic cardiac transplantation. The patient developed biventricular failure due to idiopathic myocarditis. She has had persistent New York Heart Association class IV symptoms refractory to maximal medical therapy and was placed on the transplant waiting list. An ABO-compatible cadaveric heart is available for transplant with partial human leukocyte antigen (HLA) mismatch. Cardiac transplantation is performed and the patient's T lymphocytes quickly recognize the foreign HLA molecules of the transplant cells. Inhibition of which of the following substances would specifically reduce the proliferation and differentiation of these T lymphocytes?

A. Bcl-2
B. Calcineurin
C. E-cadherin
D. Neurofibromin
E. p53

Submit

A 56-year-old woman with a history of heart failure is admitted to the hospital for orthotopic cardiac transplantation. The patient developed biventricular failure due to idiopathic myocarditis. She has had persistent New York Heart Association class IV symptoms refractory to maximal medical therapy and was placed on the transplant waiting list. An ABO-compatible cadaveric heart is available for transplant with partial human leukocyte antigen (HLA) mismatch. Cardiac transplantation is performed and the patient's T lymphocytes quickly recognize the foreign HLA molecules of the transplant cells. Inhibition of which of the following substances would specifically reduce the proliferation and differentiation of these T lymphocytes?

- A. Bcl-2 (14%)
- ✓ B. Calcineurin (71%)
- C. E-cadherin (8%)
- D. Neurofibromin (1%)
- E. p53 (3%)

Omitted
Correct answer
B

71%
Answered correctly

02 secs
Time Spent

06/27/2020
Last Updated

Explanation

Mechanism of action of common immunosuppressants

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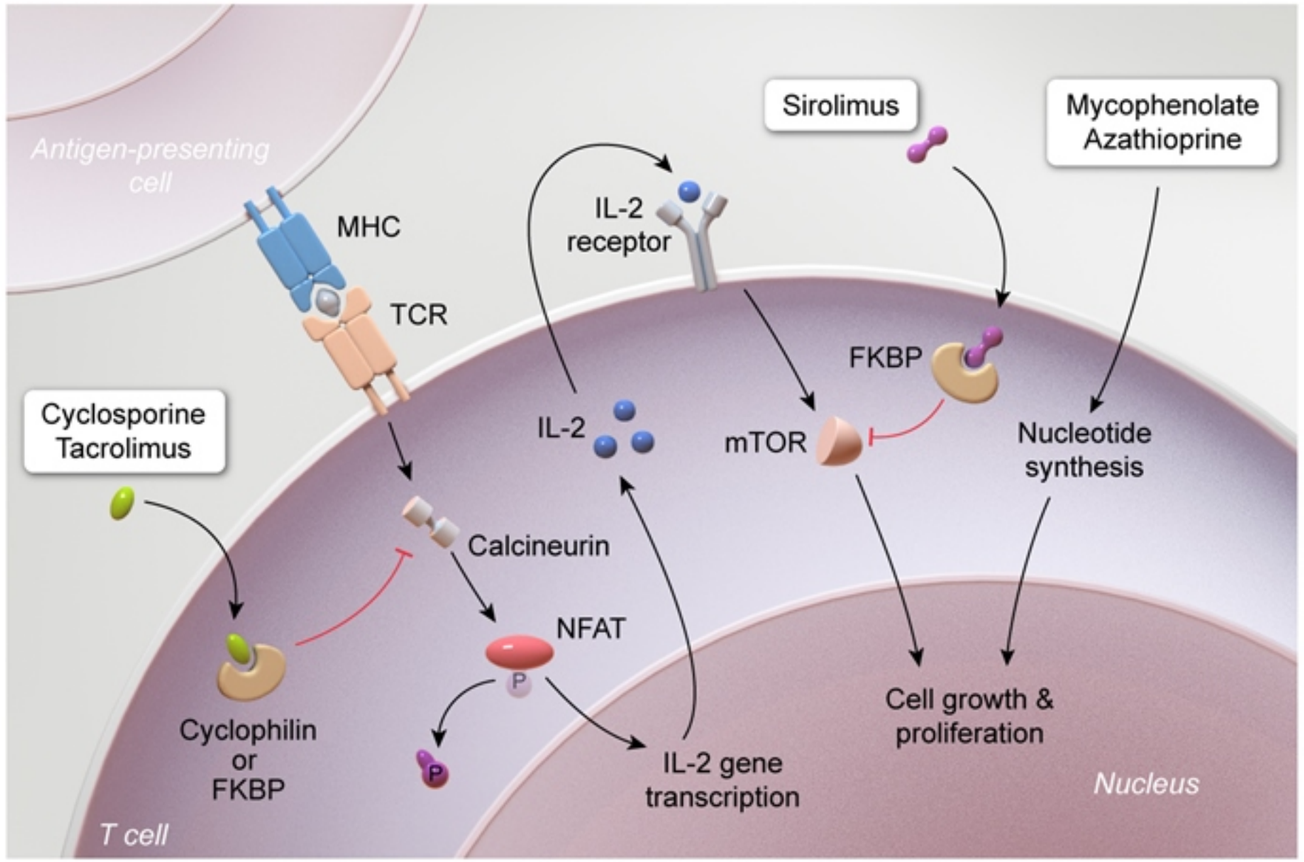
Mechanism of action of common immunosuppressants



FKBP = FK506-binding protein; **MHC** = major histocompatibility complex; **mTOR** = mammalian target of rapamycin; **NFAT** = nuclear factor of activated T cells; **TCR** = T cell receptor.

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In normal T cells, **calcineurin** is a protein phosphatase that is activated upon stimulation of the appropriate cell receptor. Once activated, calcineurin dephosphorylates nuclear factor of activated T cells (NFAT), which allows NFAT to enter the nucleus and bind to an interleukin-2 (IL-2) promoter. IL-2 stimulates the growth and differentiation of T cells and is an important component of the immune response. **Cyclosporine** and **tacrolimus**, 2 of the more commonly used immunosuppressants in transplant patients, **inhibit** calcineurin activation.

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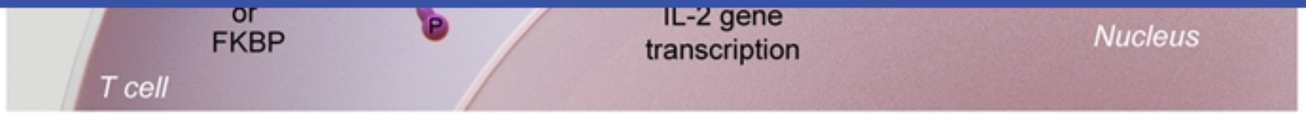

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(Choice A) Bcl-2 is an apoptosis inhibitor. When Bcl-2 is overexpressed, cell death is delayed and an accumulation of indolent malignant cells occurs. Bcl-2 involvement has been implicated in follicular cell lymphomas, most of which have a characteristic t(14;18) translocation. Bcl-2 inhibition would not be specific to T cells.

(Choice C) E-cadherin is a transmembrane glycoprotein that orchestrates epithelial cell adhesion. If this glycoprotein is lost, cell clusters may be disrupted. The loss of e-cadherin is associated with metastasis and is a predictor of disease progression in some cancers.

(Choice D) Neurofibromin is a tumor suppressor protein encoded by the *NF1* gene on chromosome 17. Neurofibromin can protect against cancer as it is a key suppressor of Ras, one of the more powerful activators of cell growth and proliferation.

(Choice E) p53 is a tumor suppressor that causes cell cycle arrest and apoptosis. It is rendered ineffective in the majority of cancers.

Educational objective:
Calcineurin is an essential protein in the activation of interleukin-2, which promotes the growth and differentiation of T cells. Immunosuppressants such as cyclosporine and tacrolimus work by inhibiting calcineurin activation.

Immunology	Allergy & Immunology	Calcineurin inhibitors
Subject	System	Topic

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Researchers are studying various cellular processes in normal and diseased states to find new anticancer drug targets. They develop a medication that inhibits an intracellular enzyme that converts adenosine to inosine. With drug use, accumulation of enzyme substrates in the neoplastic cells leads to DNA strand breaks and subsequent apoptosis. Which of the following malignancies is likely to be most responsive to this medication?

A. Hairy cell leukemia
B. Malignant melanoma
C. Ovarian teratoma
D. Small cell lung cancer
E. Soft tissue sarcoma

Submit

Researchers are studying various cellular processes in normal and diseased states to find new anticancer drug targets. They develop a medication that inhibits an intracellular enzyme that converts adenosine to inosine. With drug use, accumulation of enzyme substrates in the neoplastic cells leads to DNA strand breaks and subsequent apoptosis. Which of the following malignancies is likely to be most responsive to this medication?

- ✓ A. Hairy cell leukemia (56%)
- B. Malignant melanoma (18%)
- C. Ovarian teratoma (6%)
- D. Small cell lung cancer (13%)
- E. Soft tissue sarcoma (5%)

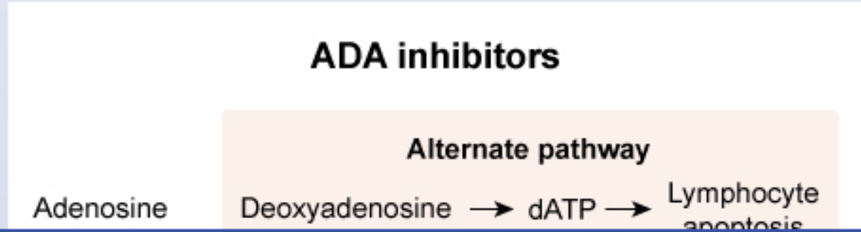
Omitted
Correct answer
A

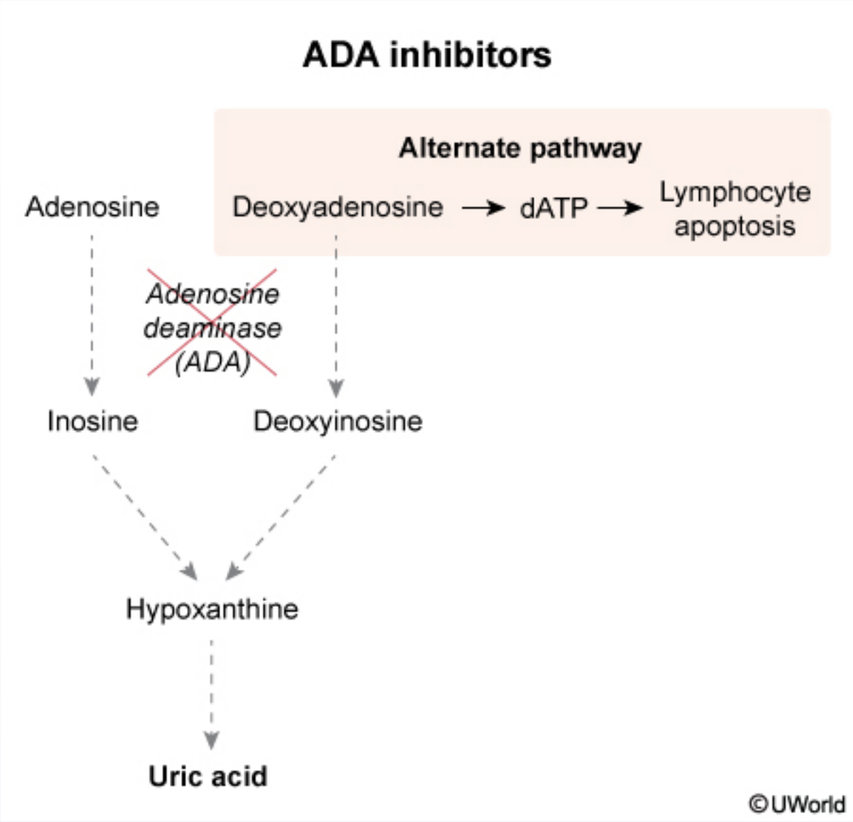
56%
Answered correctly

02 secs
Time Spent

02/02/2020
Last Updated

Explanation





Adenosine deaminase (ADA) is a highly conserved enzyme that plays a crucial role in purine metabolism. ADA removes the amino group from **adenosine**/deoxyadenosine and replaces it with a keto group, leading to the formation of **inosine**/deoxyinosine. These compounds are subsequently converted into nontoxic waste products (hypoxanthine and uric acid) and are excreted.

ADA inhibition results in the metabolism of deoxyadenosine through an alternate pathway, whereby it is phosphorylated into the **toxic metabolite** deoxyadenosine triphosphate. Elevated intracellular levels of deoxyadenosine triphosphate activate the caspase system and also inhibit ribonucleotide reductase from converting ribonucleotides to deoxyribonucleotides, which depletes cells of DNA precursors. This ultimately results

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Although all human cells contain ADA, developing lymphocytes are among the most mitotically active cells; the inhibition/absence of ADA is highly **lymphocytotoxic**. Therefore, ADA inhibitors (eg, cladribine) can be used to treat **lymphocyte-derived cancers** such as hairy cell leukemia. Similarly, children born with mutations to both ADA genes have dramatic B- and T-lymphocyte impairment, leading to the most severe form of **severe combined immunodeficiency**.

(Choices B, C, and E) Malignant melanoma is an aggressive melanocyte tumor that metastasizes early and is associated with high mortality rates when diagnosed at an advanced stage. Ovarian teratoma is an ovarian germ cell tumor that can be benign (mature) or malignant (immature). Soft tissue sarcoma is a mesenchymal tumor that tends to grow slowly over time. These tumors are not derived from lymphocyte cells and are not generally responsive to ADA inhibition.

(Choice D) Small cell lung cancer is a fast-growing neuroendocrine tumor that is most common in smokers. Fast-growing tumors are more likely to express elevated levels of ADA; however, ADA inhibition is primarily cytotoxic to lymphocyte-derived tumors and has not been shown to be of significant benefit to other cancer types.

Educational objective:
Adenosine deaminase (ADA) inhibition/absence is highly lymphocytotoxic. Medications that block ADA are used to treat lymphocyte-derived cancers. Inherited gene mutations in ADA lead to the autosomal recessive disease of severe combined immunodeficiency.

Subject	System	Topic
Immunology	Allergy & Immunology	Severe combined immunodeficiency disease

A 4-year-old male is exposed to latex gloves during a minor surgical procedure and is subsequently found to produce anti-latex IgM antibodies. Several months later he develops a severe allergic reaction to latex and is found to have a high level of serum anti-latex IgE antibodies. Which of the following cytokines is most likely responsible for this anti-latex antibody isotype change?

- A. IL-1
- B. IL-2
- C. IL-3
- D. IL-4
- E. IL-10
- F. IL-12

Submit

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- A. IL-1 (1%)
- B. IL-2 (4%)
- C. IL-3 (2%)
- ✓ D. IL-4 (85%)
- E. IL-10 (3%)
- F. IL-12 (3%)

Omitted
Correct answer
D

85%
Answered correctly

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Time Spent

04/07/2020
Last Updated

Explanation

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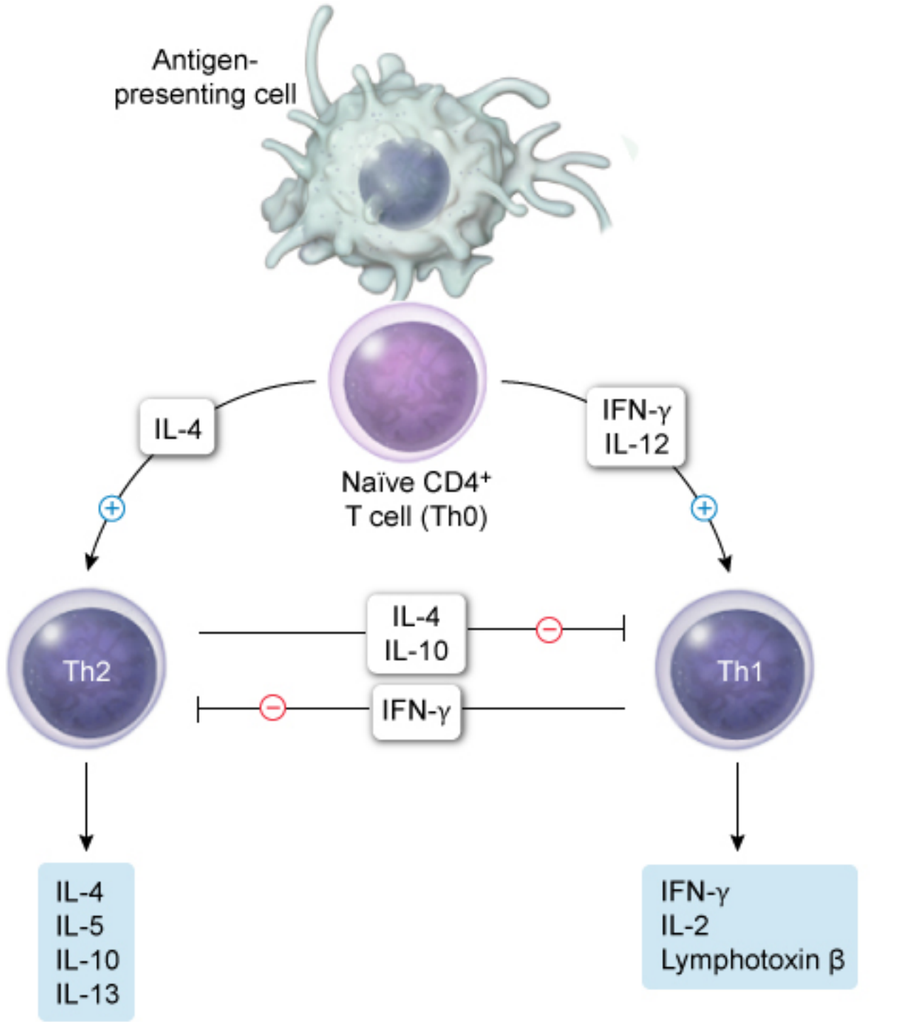
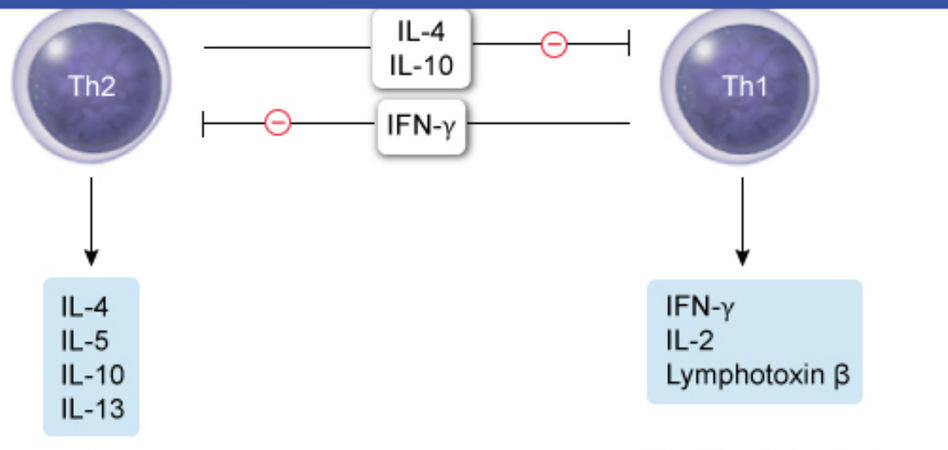
Factors in T helper cell differentiation



- Initiation of antibody response
- Activation of macrophages



IFN-γ = interferon-gamma.

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This patient has a **severe allergic reaction** to latex several months after initial sensitization. During the first encounter with an antigen (allergen), antigen-presenting cells (eg, macrophages, B cells, and dendritic cells) take up the antigen and display it with MHC class II molecules. CD4+ T cells are activated when they detect the MHC class II-associated antigen and differentiate into either T_H1 or T_H2 subsets. T_H2 lymphocytes promote the humoral immune response by secreting IL-4 and IL-5, cytokines that activate B cells.

IL-4 stimulates the **proliferation and differentiation** of T_H0 (naïve) T cells into T_H2 lymphocytes, thus increasing the T_H2 subpopulation and the stimulus for the primary humoral immune response (eg, IgM). It also induces B cell proliferation and immunoglobulin **class switching to IgE** which is responsible for the **type I hypersensitivity** reaction following repeated exposure to an allergen. IL-5 contributes to B cell differentiation in addition to its role in stimulating IgA production and eosinophil activity (eg, host defense against parasitic infections).

(Choice A) IL-1 is produced by macrophages. It activates naïve T_H0 lymphocytes and promotes their differentiation into T_H1 and T_H2 subpopulations. IL-1 is also an endogenous pyrogen.

(Choice B) IL-2 is the first interleukin produced by T cells after contact with antigen. It is secreted mainly by T_H1 cells and stimulates

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(Choice B) IL-2 is the first interleukin produced by T cells after contact with antigen. It is secreted mainly by T_H1 cells and stimulates development of CD4+ T helper cells, CD8+ cytotoxic cells, and B cells.

(Choice C) IL-3 stimulates growth and differentiation of bone marrow stem cells and is produced by T helper cells.

(Choice E) IL-10 helps regulate the balance between the T_H1 and T_H2 subpopulations of T helper cells. It is produced by T_H2 lymphocytes and inhibits synthesis of interferon-γ leading to a decrease in the T_H1 subpopulation. IL-10 also plays a part in class switching from IgM to IgG antibodies.

(Choice F) IL-12 is synthesized by macrophages and stimulates growth and development of the T_H1 subpopulation of T helper cells.

Educational Objective:
IL-4 is produced by the T_H2 subset of T helper cells. It facilitates proliferation of B cells and T_H2 lymphocytes and stimulates antibody isotype switching to IgE which mediates type I hypersensitivity (allergic) reactions.

Immunology	Allergy & Immunology	Latex Allergy
Subject	System	Topic

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Immunology	Allergy & Immunology	Latex Allergy
Subject	System	Topic

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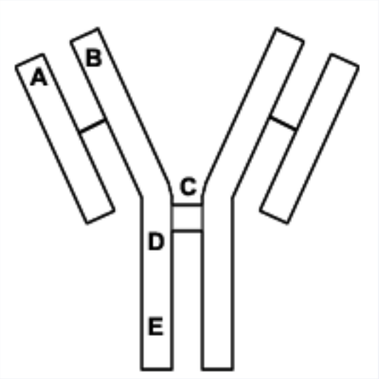
IgG autoantibodies against a RBC antigen that are found in a 34-year-old Caucasian female are able to cause cell lysis after binding the C1 complement component. Which of the following is the complement binding site for the immunoglobulin molecule shown on the slide below?



- A. A
- B. B
- C. C
- D. D
- E. E

Submit

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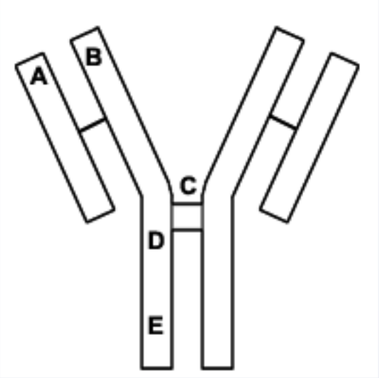


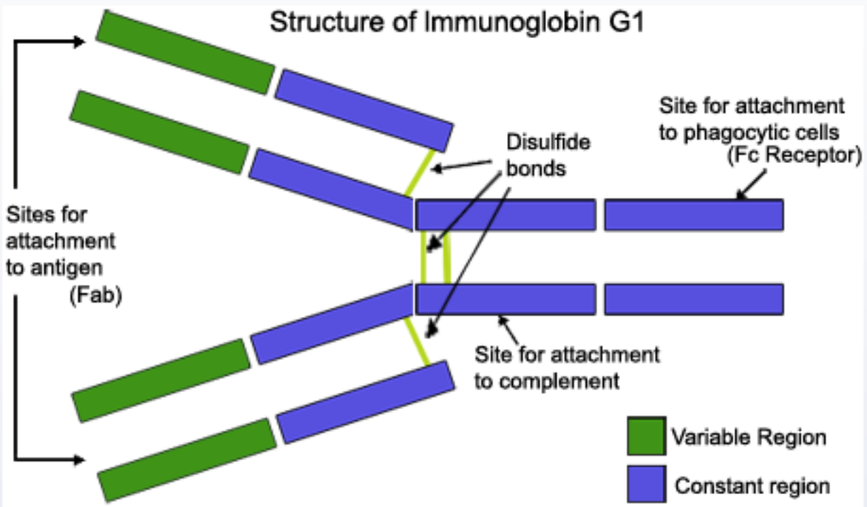
- A. A (8%)
- B. B (7%)
- C. C (5%)
- ✓ D. D (43%)
- E. E (34%)

Omitted
Correct answer
D

43%
Answered correctly

02 secs
Time Spent

02/03/2020
Last Updated



Both IgG antibodies and IgM antibodies are capable of, and essential for, triggering the classical complement pathway after binding a C1 molecule. The classical pathway would not be able to proceed in the absence of either IgM or IgG. C1 is the complement component that when activated is able to release the catalytic factors responsible for the next steps in the classical complement pathway. In order to be activated, C1 must bind the Fc portions of two different antibodies at specific C1 binding sites. Because IgM circulates in pentameric form (five IgM molecules joined together at their Fc regions by a J chain peptide), it is much more effective in initiating the complement cascade than IgG which circulates in monomeric form (a single circulating immunoglobulin as pictured above). The complement binding site on both IgG and IgM is located in the Fc portion closer to the hinge region **(Choice D)**. Activation of complement by IgM prior to antigen binding is prevented due to the fact that the C1 binding site on IgM is hidden while unbound IgM is circulating in its planar form. A conformational change in the IgM molecule after antigen binding results in exposure of the C1 binding site.

(Choices A and B) Choices A and B indicate the hypervariable regions of the Fab (antigen binding fragment) portion of the light chain and heavy chain of the IgG molecule, respectively. These regions of the immunoglobulin protein are also referred to as the complementarity-determining regions of the antibody because their structure determines what complementary protein antigen will be bound by the antibody.

(Choice C) The area indicated by the letter C represents the two disulfide bonds that hold the heavy chains of the immunoglobulin together just before the hinge region of the molecule.

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(Choice C) The area indicated by the letter C represents the two disulfide bonds that hold the heavy chains of the immunoglobulin together just before the hinge region of the molecule.

(Choice E) The region marked by the letter E represents the Fc receptor binding site on the constant region of the heavy chain of the IgG immunoglobulin molecule. On an IgM or an IgA molecule this region may additionally indicate the binding site for the J chain that is able to bind these immunoglobulins in their dimeric (IgA) or pentameric (IgM) forms.

Educational Objective:
The classical complement cascade begins with binding of the C1 complement component to either two molecules of IgG or to two molecules of IgM. Because IgM circulates in pentameric form, it is a much better activator of the complement system. The C1 molecule binds to the Fc region of the heavy immunoglobulin chain in the region near the hinge point.

Immunology	General Principles	Immunoglobulins
Subject	System	Topic

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The acidification of lysosomes within antigen presenting cells is prevented in an experimental setting. The affected cells show impaired interaction with T lymphocytes upon antigen exposure. The observed effect most likely results from a low cell surface expression of which of the following molecules?

- A. Cytokine receptors
- B. Integrins
- C. MHC class I
- D. MHC class II
- E. T cell receptor

Submit

The acidification of lysosomes within antigen presenting cells is prevented in an experimental setting. The affected cells show impaired interaction with T lymphocytes upon antigen exposure. The observed effect most likely results from a low cell surface expression of which of the following molecules?

- A. Cytokine receptors (4%)
- B. Integrins (2%)
- C. MHC class I (20%)
- ✓ D. MHC class II (59%)
- E. T cell receptor (12%)

Omitted
Correct answer
D

59%
Answered correctly

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04/12/2020
Last Updated

Explanation

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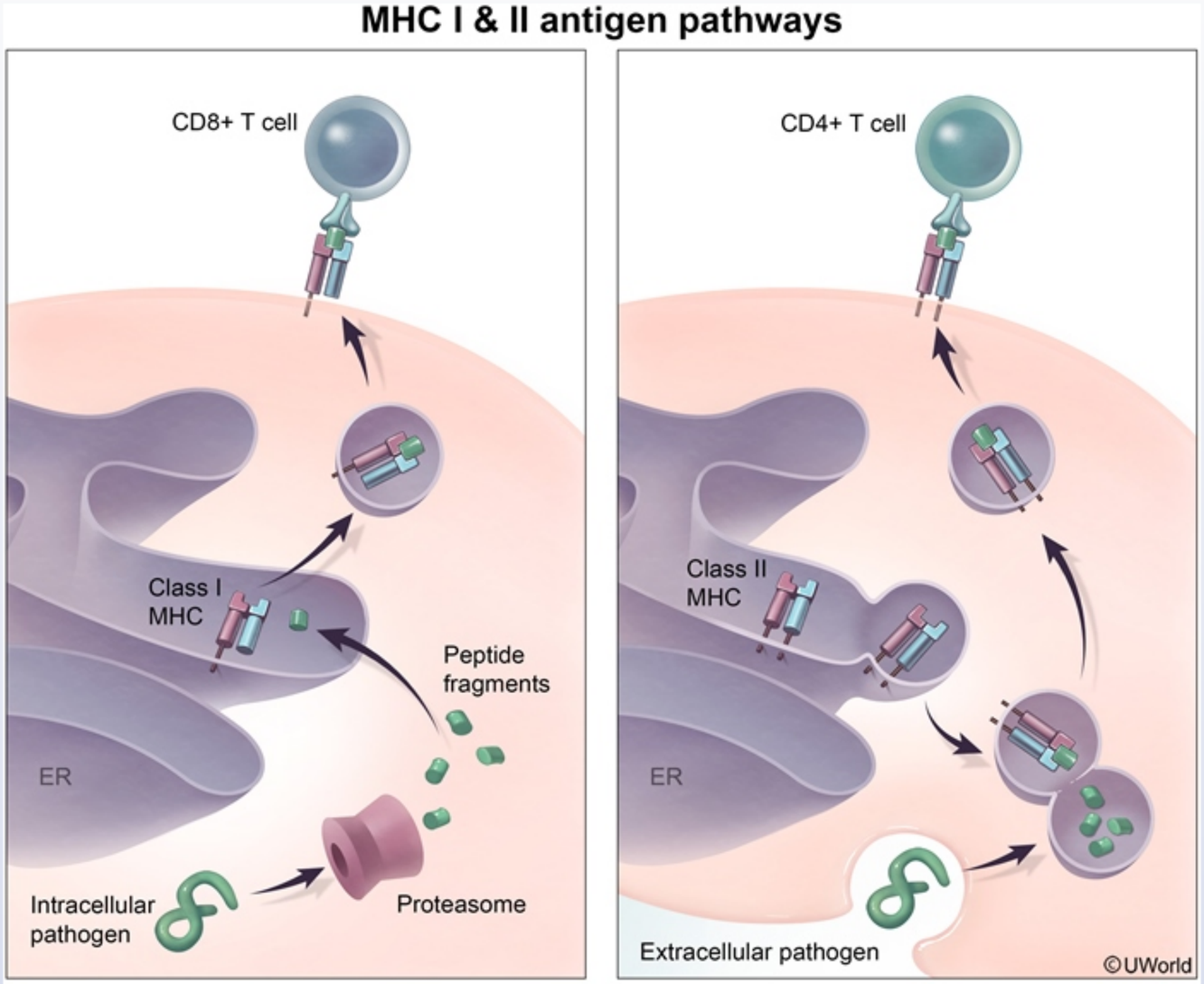

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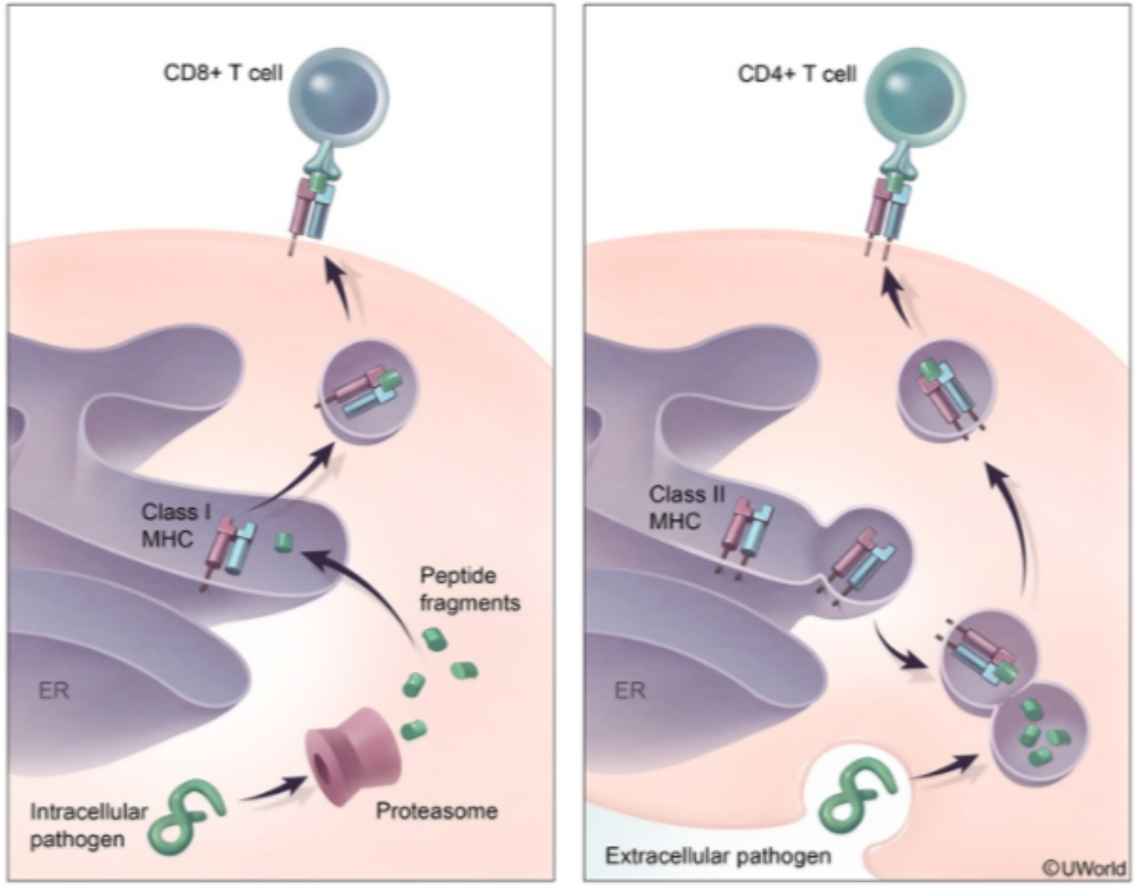
MHC I & II antigen pathways



Class I MHC pathway

Class II MHC pathway

Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

Antigen presenting cells (eg, dendritic cells, macrophages, B lymphocytes) present **extracellular antigens** (eg, bacterial, viral) on **MHC class II molecules**. After phagocytosis or endocytosis, the protein is degraded in **acidified lysosomes** and the antigen is loaded onto an MHC class II molecule.

The MHC class II-antigen complexes are then displayed on the surface of antigen presenting cells where they can bind to T cell receptors (TCR) to initiate a **T cell response** to the antigen. Without lysosomal acidification, exogenous antigen processing and association with MHC class II molecules would not occur, resulting in **impaired interaction** between antigen presenting cells and T cells.

(Choice A) Cytokine receptors are responsible for exerting the biological effects of the various cytokines (eg, interferons, chemokines, tumor necrosis factors). Expression of these receptors does not depend on lysosomal acidification and would not directly affect T cell binding to antigen presenting cells.

(Choice B) Integrins are necessary for the binding of inflammatory cells to vascular walls during the process of transmigration through the endothelial layer from the bloodstream to tissues.

(Choice C) Most nucleated cells of the human body express MHC Class I molecules on their surfaces. MHC Class I molecules present intracellular antigens produced in tumor or virus-infected cells. Cytoplasmic proteins are degraded by a proteasome and transported into the rough endoplasmic reticulum (via TAP proteins) where they are loaded onto MHC Class I molecules and routed to the cell surface. This pathway does not depend on acidified lysosomes.

(Choice E) The T cell receptor (TCR) is a membrane-bound protein on T cells that is responsible for recognizing specific antigens bound to an MHC molecule. Although the TCR is essential for T cell activation in response to antigens presented on MHC Class II molecules, prevention of lysosome acidification would have no effect on the expression of TCR on the surface of T cells.

Educational objective:
MHC class II is expressed on the surface of antigen presenting cells (APC) and presents extracellular antigens to T cells after extracellular protein is degraded within acidified lysosomes. Failure to acidify lysosomes would lead to deficient expression of MHC class II-antigen complexes with subsequent impaired interaction between APCs and T cells.

Immunology General Principles Major histocompatibility class

On flow cytometric analysis of a sample of fetal thymus, a certain population of cells is identified that is positive for both CD4 and CD8 cell surface antigens. These cells are best characterized as which of the following cells?

- A. Immature cortical T lymphocytes
- B. Mature cytotoxic T lymphocytes
- C. Mature helper T lymphocytes
- D. Antigen presenting cells
- E. Natural killer (NK) cells
- F. Thymic epithelial cells

Submit

On flow cytometric analysis of a sample of fetal thymus, a certain population of cells is identified that is positive for both CD4 and CD8 cell surface antigens. These cells are best characterized as which of the following cells?

- ✓ A. Immature cortical T lymphocytes (87%)
- B. Mature cytotoxic T lymphocytes (2%)
- C. Mature helper T lymphocytes (3%)
- D. Antigen presenting cells (2%)
- E. Natural killer (NK) cells (1%)
- F. Thymic epithelial cells (2%)

Omitted
Correct answer
A

87%
Answered correctly

02 secs
Time Spent

02/03/2020
Last Updated

Explanation

T-lymphocytes, or thymocytes, are produced in the bone marrow and undergo maturation in the thymus during the first trimester of gestation. In the thymus the processes of T-cell receptor (TCR) gene rearrangement, positive selection, negative selection and expression of extracellular membrane markers and co-stimulatory molecules occur. Pro-T cells arrive at the thymus as "double negative" cells - cells that lack both CD4 and CD8 antigens. Next, the process of TCR gene rearrangement begins first with rearrangement of the β chain genes. Synthesis of a productive rearrangement of the β chain of the TCR leads to stimulation of production of BOTH CD4 and CD8 antigens with simultaneous expression of BOTH CD4 and CD8. These cells are referred to as "double positive" T cells or immature T-lymphocytes **(Choice A)**. Subsequently, the process

T-lymphocytes, or thymocytes, are produced in the bone marrow and undergo maturation in the thymus during the first trimester of gestation. In the thymus the processes of T-cell receptor (TCR) gene rearrangement, positive selection, negative selection and expression of extracellular membrane markers and co-stimulatory molecules occur. Pro-T cells arrive at the thymus as "double negative" cells - cells that lack both CD4 and CD8 antigens. Next, the process of TCR gene rearrangement begins first with rearrangement of the β chain genes. Synthesis of a productive rearrangement of the β chain of the TCR leads to stimulation of production of BOTH CD4 and CD8 antigens with simultaneous expression of BOTH CD4 and CD8. These cells are referred to as "double positive" T cells or immature T-lymphocytes **(Choice A)**. Subsequently, the process of rearrangement of the α chain of the TCR occurs followed by positive selection in the thymic cortex and negative selection in the thymic medulla. Once these processes are complete, the final step in maturation of the T-lymphocytes is loss of either the CD4 or the CD8 antigen so that the mature thymocytes only express one or the other of these antigens.

(Choice B) Mature cytotoxic T lymphocytes (CTLs) are also referred to as CD8+ T-lymphocytes; these cells do not express the CD4 antigen on their surfaces. These cells recognize and kill altered self cells by recognizing foreign antigen presented by these cells on MHC Class I molecules on the cell surface.

(Choice C) Mature helper T lymphocytes are also referred to as CD4+ T-lymphocytes; these cells do not express the CD8 antigen on their surfaces.

(Choice D) Antigen presenting cells include dendritic cells, macrophages and B-lymphocytes. Dendritic cells are professional antigen presenting cells. They take up antigen by endocytosis, constitutively express MHC Class II and the co-stimulatory B7 molecule, and are able to activate all forms of T cells (naïve, effector and memory). Macrophages are phagocytes that only inducably express MHC II and B7 and can only activate effector and memory T cells, not naive T cells. B-lymphocytes take up antigen by receptor-mediated (membrane-bound antibody) endocytosis and constitutively express MHC II. These cells are able to stimulate all forms of T-lymphocytes.

(Choice E) Natural killer (NK) cells are part of the innate immune system and function in a fashion very similar to CD8+ CTLs though they express neither CD8 nor CD4 on their cell surfaces.

(Choice F) Thymic epithelial cells play a role in positive selection of immature thymocytes in the thymic cortex. These cells express MHC antigens on their cell surfaces that interact with the TCR on the immature thymocytes. Thymocytes able to bind MHC receive a protective signal and do not undergo apoptosis, while thymocytes unable to bind MHC will be killed. This is how self-MHC restriction is generated in the T-lymphocyte population.

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Educational Objective:
Immature T-lymphocytes express both the CD4 and CD8 cell surface antigens in addition to a complete TCR or a pro-TCR. These lymphocytes exist in the thymic cortex where they undergo positive selection and in the thymic medulla where they undergo negative selection.

Immunology	General Principles	Cell mediated immunity
Subject	System	Topic

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A researcher identifies a group of malignant epithelial cells in the sigmoid colon that have decreased their surface expression of MHC class I antigen. Which of the following immune effector cell types is most likely to kill the transformed epithelial cells?

- A. Neutrophils
- B. Macrophages
- C. Dendritic cells
- D. CD4+ T lymphocytes
- E. Plasma cells
- F. Natural killer cells

Submit

A researcher identifies a group of malignant epithelial cells in the sigmoid colon that have decreased their surface expression of MHC class I antigen. Which of the following immune effector cell types is most likely to kill the transformed epithelial cells?

- A. Neutrophils (1%)
- B. Macrophages (6%)
- C. Dendritic cells (1%)
- D. CD4+ T lymphocytes (5%)
- E. Plasma cells (1%)
- ✓ F. Natural killer cells (84%)

Omitted
Correct answer
F

84%
Answered correctly

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02/03/2020
Last Updated

Explanation

Natural killer (NK) cells are responsible for the destruction of cells with decreased or absent MHC class I proteins on their surfaces. Such changes in MHC I antigen expression occur in virus-infected cells and tumor cells. Natural killer cells are derived from lymphoid stem cells and comprise approximately 10% of all circulating lymphocytes. They are large cells with cytoplasmic granules containing perforins, which produce holes in target cell membranes, and granzymes, chemicals that induce target cell apoptosis. Granzymes gain access to the target cell via membrane holes created by perforin. The target cell subsequently undergoes apoptosis. NK cells do not directly lyse cells.

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NK cells:

1. Do not express CD4, CD8 or CD3 molecules on their surface. They do express either CD16 or CD 56.
2. Do not require the thymus for maturation and are present in athymic patients.
3. Have no antigen-specific activities, do not require exposure to antigen for activation, and do not possess antigen memory ability.
4. Are activated by interferon-γ and IL-12.

(Choice A) Neutrophils do not directly kill malignant cells.

(Choice B) The functions of macrophages include phagocytosis, antigen presentation to T-helper lymphocytes in association with MHC class II molecules, and secretion of immunomodulatory cytokines, like TNF and IL-1.

(Choice C) Dendritic cells are avid antigen presenting cells that constantly sample their environment by endocytosis and become activated upon encountering a foreign antigen. When activated, dendritic cells migrate to the lymph nodes and spleen where they display antigen with MHC II and co-stimulatory molecules to activate T-cells and B-cells.

(Choice D) CD4+ T-lymphocytes (T_H cells) are activated by antigen presented in association with MHC II molecules and can promote cell-mediated (macrophages and $CD8^+$ cells) and/or humoral (B-cells) immune responses.

(Choice E) B-cells transform into plasma cells under the influence of activated T_H cells. Plasma cells secrete antigen-specific immunoglobulins.

Educational Objective:
NK cells recognize and kill cells with decreased MHC class I antigen cell surface expression, such as virus-infected cells and tumor cells. They are large lymphocytes that contain perforins and granzymes in cytoplasmic granules. NK cells kill target cells by inducing apoptosis.

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NK cells recognize and kill cells with decreased MHC class I antigen cell surface expression, such as virus-infected cells and tumor cells. They are large lymphocytes that contain perforins and granzymes in cytoplasmic granules. NK cells kill target cells by inducing apoptosis.

Immunology	General Principles	Cell mediated immunity
Subject	System	Topic

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Foreign antigen recognition at the cell surface by cytotoxic T-lymphocytes stimulates a response that results in rapid cell death. Which of the following act as effectors of this response?

A. Matrix metalloproteinases

B. Acid hydrolases

C. Caspases

D. Phospholipase A_2

E. Protein kinase A

Submit

Foreign antigen recognition at the cell surface by cytotoxic T-lymphocytes stimulates a response that results in rapid cell death. Which of the following act as effectors of this response?

- A. Matrix metalloproteinases (6%)
- B. Acid hydrolases (9%)
- ✓ C. Caspases (78%)
- D. Phospholipase A_2 (3%)
- E. Protein kinase A (2%)

Omitted
Correct answer
C

78%
Answered correctly

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02/03/2020
Last Updated

Explanation

The two primary modes of cell death are necrosis (which is induced by injury) and apoptosis (which is initiated by the host organism in response to cell damage, age-related atrophy, or specific stages of embryogenesis). Apoptosis is helpful in the elimination of cells that are no longer necessary and in the maintenance of a constant number of cells in rapidly growing tissues. Tumor cells, for example, die by apoptosis. The death of B and T lymphocytes and virally-infected cells also occurs through apoptosis. The remains of cells that die by this method are phagocytized by macrophages.

The process of apoptosis involves the following steps:

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The process of apoptosis involves the following steps:

1. Initiation: Apoptosis is triggered by different stimuli and can occur through either the intrinsic, mitochondria-mediated pathway or the extrinsic, receptor-initiated pathway. Cells damaged by ultraviolet light, heat, hypoxia, toxins, or radiation display intrinsic apoptotic signals (eg, phosphatidylserine or thrombospondin) on their plasma membranes. Extrinsic apoptosis, in contrast, is induced by the tumor necrosis factor (TNF) when bound to tumor necrosis factor receptor 1 (TNFR1) or the Fas ligand when bound to cell surface receptor Fas.
2. Control: Intrinsic apoptosis is mediated by a group of bcl-2 proteins. Some of the components of this system are pro-apoptotic (eg, Bak, Bax, and Bim proteins), while others are anti-apoptotic (eg, Bcl-x and Bcl-2 proteins). Apoptotic signals tip the balance between these two forces, resulting in changes of the inner mitochondrial membrane. These changes are responsible for the formation of the mitochondrial permeability transition (MPT) and the release of cytochrome c and other pro-apoptotic proteins into the cytoplasm, which then activate caspases. In extrinsic apoptosis, the binding of the death ligand and the death receptor allows for pro-caspase molecules to be brought into close proximity.
3. Destruction: Both the intrinsic and extrinsic pathways converge at this step, resulting in caspase activation. Caspases are proteolytic enzymes that destroy cell components. They contain cysteine and are able to cleave aspartic acid residues (**c**ysteine-**asp**artic-acid-prote**ases**). The eleven caspases that have been identified are classified as either initiator or effector caspases. Initiator caspases activate the effector caspases, which then cleave the cellular proteins.

(Choice A) Metalloproteinases are zinc-containing enzymes that degrade the components of the extracellular matrix (eg, collagen, laminin, fibronectin). Metalloproteinases are essential for proper tissue remodeling during wound healing.

(Choice B) Acid hydrolases do not participate in apoptosis.

(Choice D) Phospholipase A2 does not participate in apoptosis.

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(Choice E) Protein kinase A is a component of the cAMP-associated signaling system. The binding of a ligand to a G-protein-linked receptor results in adenylyl cyclase activation and the release of cAMP. Elevated levels of cAMP activate protein kinase A.

Educational Objective:
Apoptosis can occur through either the intrinsic (mitochondria-mediated) pathway or the extrinsic (receptor-initiated) pathway. Both pathways converge in the activation of caspases. Caspases are proteolytic enzymes that cleave cellular proteins.

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Immunology	General Principles	Cell mediated immunity
Subject	System	Topic

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The following vignette applies to the next **2** items. The items in the set must be answered in sequential order. Once you click **Proceed to Next Item**, you will not be able to add or change an answer.

A 52-year-old woman comes to the emergency department with pain and redness affecting her left leg. The patient's symptoms began 2 days ago and have progressed to the point where she cannot walk without experiencing severe pain. Physical examination shows a large, erythematous area with indistinct margins over her left leg. The area feels hot and indurated and is exquisitely tender. She is admitted to the hospital for severe left leg cellulitis and is started on intravenous cefazolin. Several minutes after the infusion is started, she experiences shortness of breath, diffuse itching, and dizziness. Her blood pressure is 64/38 mm Hg and heart rate is 130/min. On examination, there is a diffuse erythematous skin rash and bilateral wheezing is heard on lung auscultation.

Item 1 of 2

Which of the following is most likely to be elevated in this patient's serum as a result of her medication reaction?

- A. 5-hydroxyindoleacetic acid
- B. Alkaline phosphatase
- C. Calcitonin
- D. Myeloperoxidase
- E. Tryptase

Submit

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Item 1 of 2

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- A. 5-hydroxyindoleacetic acid (35%)
- B. Alkaline phosphatase (13%)
- C. Calcitonin (2%)
- D. Myeloperoxidase (24%)
- ✓ E. Tryptase (25%)

Omitted
Correct answer
E

25%
Answered correctly

02 secs
Time Spent

06/01/2020
Last Updated

Anaphylaxis	
Triggers	• Food (eg, nuts, shellfish) • Medications (eg, β-lactam antibiotics) • Insect stings

Clinical manifestations	• Cardiovascular
	  ◦ Vasodilation → hypotension & tissue edema
	  ◦ Tachycardia
	• Respiratory
	  ◦ Upper airway edema → stridor & hoarseness
	  ◦ Bronchospasm → wheezing
	• Cutaneous
	  ◦ Urticarial rash, pruritus, flushing
	• Gastrointestinal
	  ◦ Nausea, vomiting, abdominal pain

Treatment	• Intramuscular epinephrine • Airway management & volume resuscitation • Adjunctive therapy (eg, antihistamines, glucocorticoids)

This patient is experiencing an **anaphylactic reaction** to the cephalosporin cefazolin. Anaphylaxis is a systemic type 1 hypersensitivity reaction characterized by increased vascular permeability and **multisystem edema**, leading to massive shifting of intravascular fluid to the extravascular compartment. Symptoms often begin within seconds to minutes after intravascular exposure to an inciting factor (eg, insect stings, intravenous medications) but can take up to 2 hours to develop with orally ingested antigens.

Anaphylaxis results from widespread **mast cell and basophil degranulation** and resultant **histamine** and **tryptase** release. Tryptase is an enzyme that is relatively specific to mast cells, and elevated serum levels of tryptase are often used to support a clinical diagnosis of anaphylaxis after the patient has been stabilized.

This patient is experiencing an **anaphylactic reaction** to the cephalosporin cefazolin. Anaphylaxis is a systemic type 1 hypersensitivity reaction characterized by increased vascular permeability and **multisystem edema**, leading to massive shifting of intravascular fluid to the extravascular compartment. Symptoms often begin within seconds to minutes after intravascular exposure to an inciting factor (eg, insect stings, intravenous medications) but can take up to 2 hours to develop with orally ingested antigens.

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(Choice A) 5-hydroxyindoleacetic acid is a breakdown product of serotonin that is used to screen for carcinoid syndrome. Although mast cell granules contain some preformed serotonin, serum levels are not significantly elevated in anaphylaxis.

(Choice B) Alkaline phosphatase is present in all cells of the body, but the highest levels are found in the liver, bones, and placenta.

(Choice C) Calcitonin is produced by the C cells of the thyroid gland and can be useful as a tumor marker for medullary thyroid carcinoma.

(Choice D) Myeloperoxidase is found predominately in neutrophils. Serum levels of myeloperoxidase can increase following inflammation and infection but would not rise in response to an acute allergic reaction.

Educational objective:
Anaphylaxis is the result of widespread mast cell and basophil degranulation and the release of preformed inflammatory mediators, including histamine and tryptase. Tryptase is relatively specific to mast cells and can be used as a marker for mast cell activation.

References

- Risk assessment in anaphylaxis: current and future approaches.

Immunology	General Principles	Anaphylaxis
Subject	System	Topic

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Immunology	General Principles	Anaphylaxis
Subject	System	Topic

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Item 2 of 2

The patient's anaphylactic reaction is determined to be mediated by antigen-specific IgE antibodies attached to high-affinity receptors on the surface of mast cells and basophils. Which of the following mechanisms is most likely to trigger vasoactive substance release by these cells?

A. Antibody-receptor covalent binding

B. Antibody-receptor dissociation

C. Receptor aggregation

D. Receptor detachment from the cell surface

E. Receptor internalization

Submit

Item 2 of 2

The patient's anaphylactic reaction is determined to be mediated by antigen-specific IgE antibodies attached to high-affinity receptors on the surface of mast cells and basophils. Which of the following mechanisms is most likely to trigger vasoactive substance release by these cells?

- A. Antibody-receptor covalent binding (40%)
- B. Antibody-receptor dissociation (3%)
- ✓ C. Receptor aggregation (44%)
- D. Receptor detachment from the cell surface (4%)
- E. Receptor internalization (7%)

Omitted
Correct answer
C

44%
Answered correctly

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Explanation

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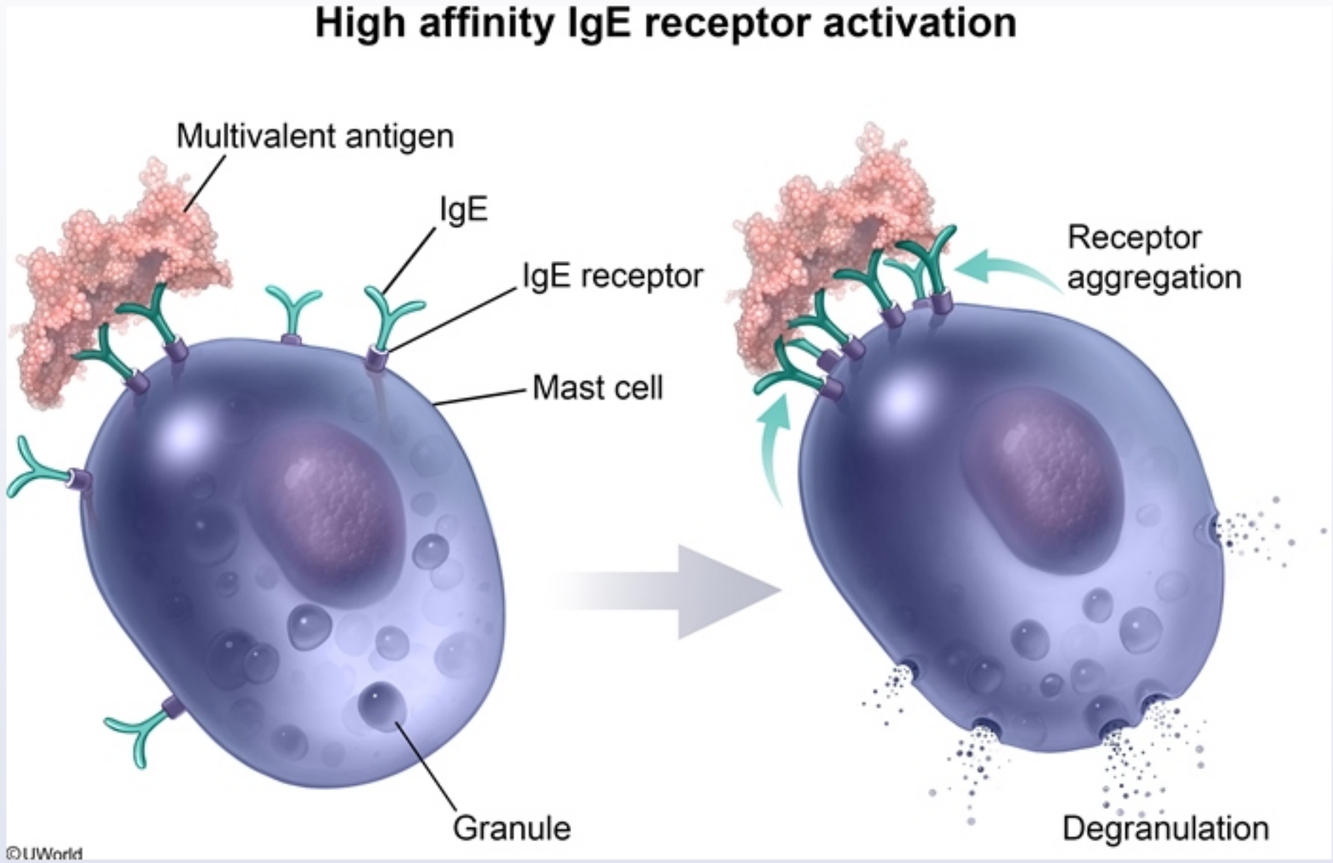

The **high-affinity IgE receptor** (FcεRI) is found on mast cells and basophils and plays a primary role in mediating the allergic response. The receptor normally binds the Fc portion of circulating IgE, coating the cell with various antigen-specific IgE molecules. When a multivalent antigen comes in contact with the cell, multiple IgE antibodies become **cross-linked**, resulting in **aggregation** of the FcεRI receptors on the mast cell surface. This clumping of receptors leads to the activation of non-receptor tyrosine kinases, triggering an intracellular cascade that ultimately results in mast cell and basophil **degranulation**.

(Choices A and B) The high strength of the IgE-FcεRI bond is a result of the sum of many weak noncovalent forces; it is not associated with the

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(Choices A and B) The high strength of the IgE-FcεRI bond is a result of the sum of many weak noncovalent forces; it is not associated with the formation of covalent (eg, disulfide, peptide) bonds. The strength of this attachment is such that antibody-receptor dissociation is rare; most of the total IgE in the body is bound to the surface of mast cells and basophils and not circulating freely.

(Choice D) Receptor detachment from the cell surface is not a known mechanism of signal transduction.

(Choice E) Receptor internalization occurs in the process of synaptic desensitization to excessive neurotransmitter stimulation. It also occurs in receptor-mediated endocytosis of substances such as iron (ie, transferrin receptor) and cholesterol (ie, LDL receptor).

Educational objective:
The high-affinity IgE receptor (FcεRI) is found on the surface of mast cells and basophils and normally binds the Fc portion of circulating IgE antibodies. Cross-linking of multiple membrane-bound IgE antibodies by a multivalent antigen results in aggregation of the FcεRI receptors, causing degranulation and the release of preformed mediators (eg, histamine, tryptase) that initiate an allergic response.

References

- Mast cell signal transduction from the high-affinity IgE receptor.

Immunology	General Principles	Anaphylaxis
Subject	System	Topic

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A 33 year-old female is being followed by her neurologist for her multiple sclerosis. She was initially diagnosed with relapsing remitting subtype after an episode of visual disturbance and an episode of paralysis. In her study of autoimmune diseases she encounters the topic of lymphocyte development and comes across a question which she poses to her neurologist during a routine follow-up visit: During the process of T-lymphocyte maturation, T cell receptors of many lymphocytes demonstrate a very high-affinity interaction with MHC molecules expressed on thymic medullary epithelial and dendritic cells. What process do these lymphocytes undergo at this time?

- A. Affinity maturation
- B. Isotype switching
- C. Negative selection
- D. Positive selection
- E. TCR DNA rearrangement

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- A. Affinity maturation (4%)
- B. Isotype switching (2%)
- ✓ C. Negative selection (63%)
- D. Positive selection (28%)
- E. TCR DNA rearrangement (1%)

Omitted
Correct answer
C

63%
Answered correctly

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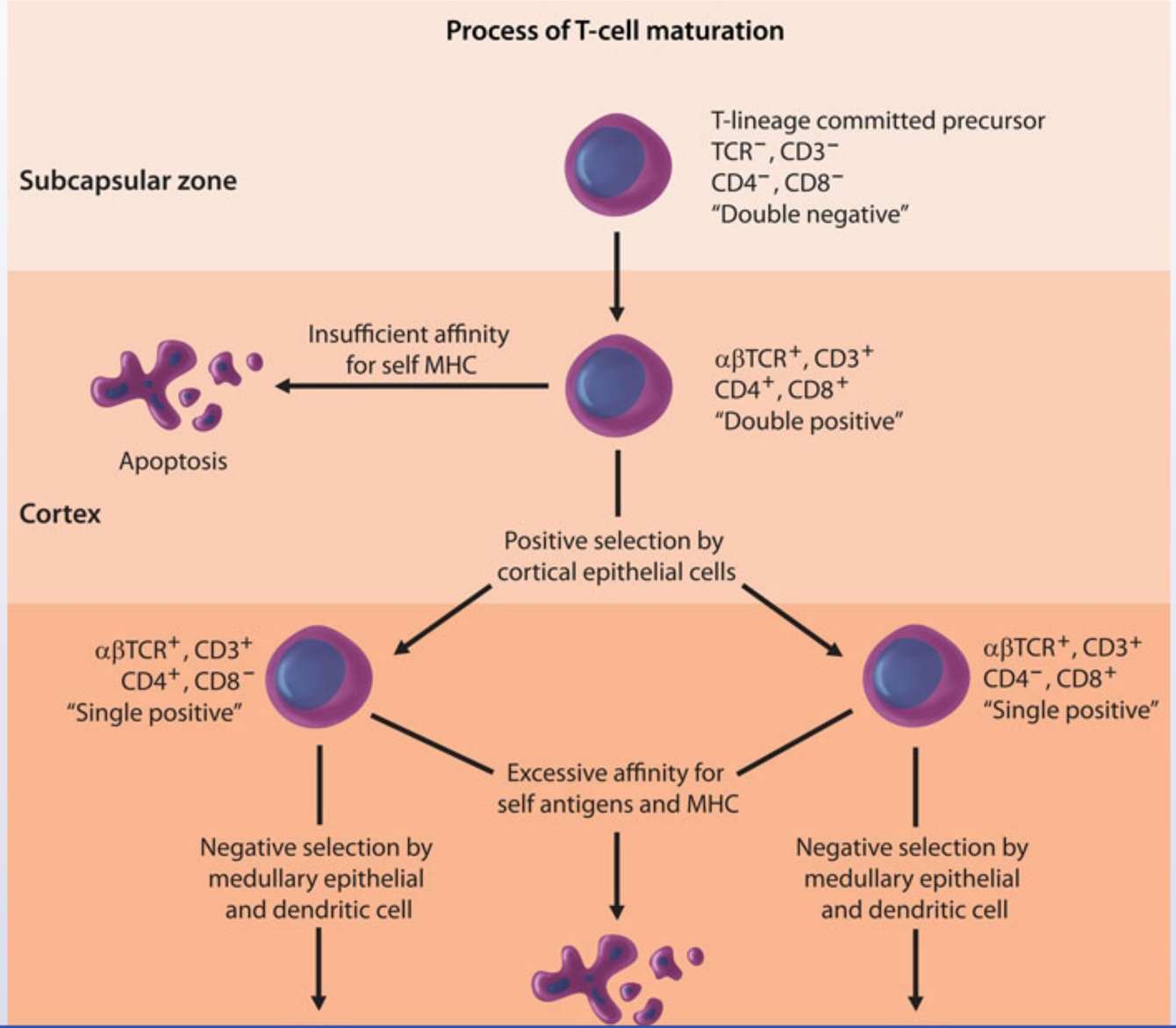
Explanation

Process of T-cell maturation

T-lineage committed precursor
$TCR^-, CD3^-$


Process of T-cell maturation
Subcapsular zone
T-lineage committed precursor
TCR⁻, CD3⁻
CD4⁻, CD8⁻
"Double negative"
Insufficient affinity
for self MHC
αβTCR⁺, CD3⁺
CD4⁺, CD8⁺
"Double positive"
Apoptosis
Cortex
Positive selection by
cortical epithelial cells
αβTCR⁺, CD3⁺
CD4⁺, CD8⁻
"Single positive"
αβTCR⁺, CD3⁺
CD4⁻, CD8⁺
"Single positive"
Excessive affinity for
self antigens and MHC
Negative selection by
medullary epithelial
and dendritic cell
Negative selection by
medullary epithelial
and dendritic cell

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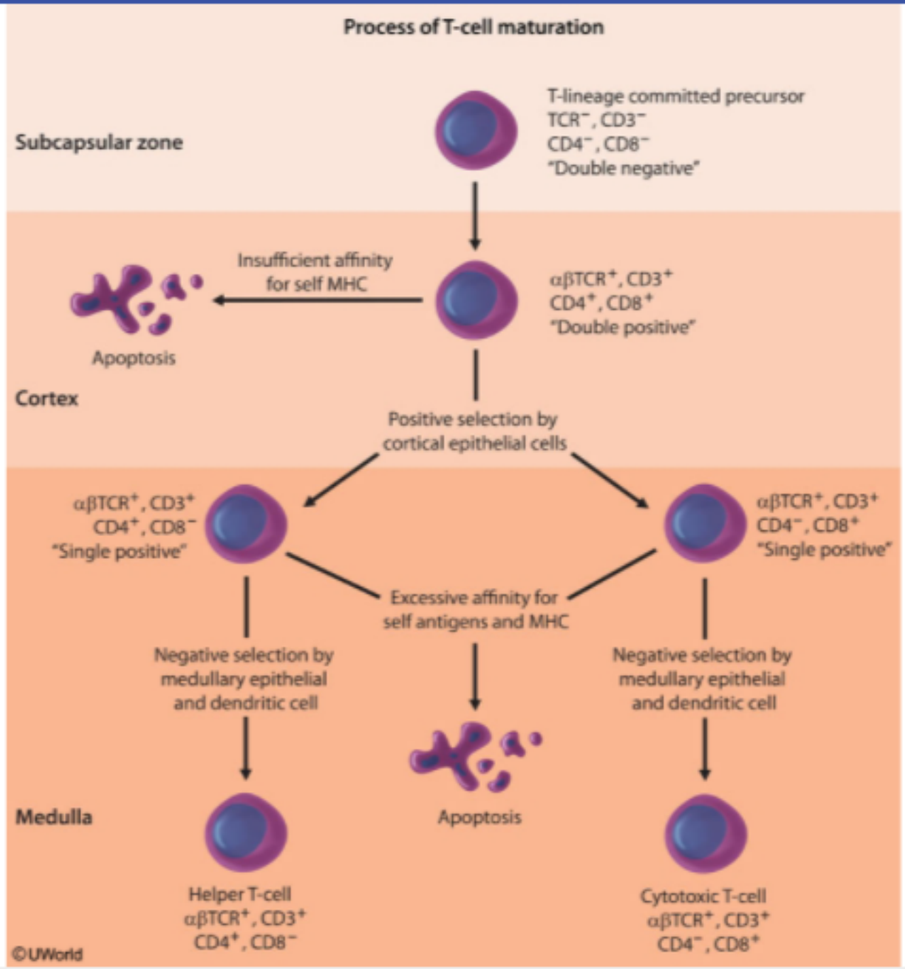

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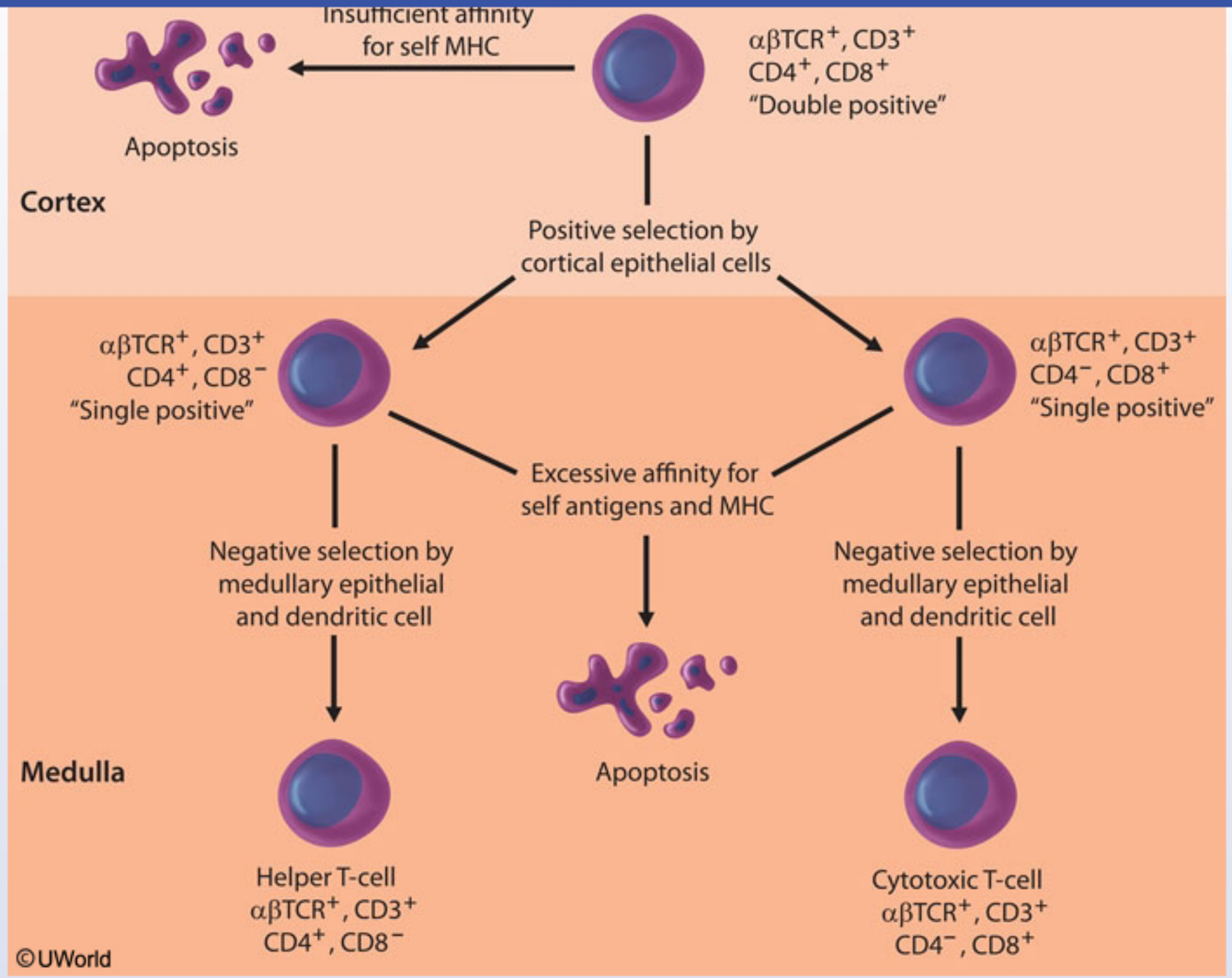

T-lymphocytes, or thymocytes, are initially produced in the bone marrow, but they migrate from that location to mature during the first trimester of gestation in the thymus. In the thymus, the processes of T-cell receptor (TCR) gene rearrangement, positive selection, negative selection, and

T-lymphocytes, or thymocytes, are initially produced in the bone marrow, but they migrate from that location to mature during the first trimester of gestation in the thymus. In the thymus, the processes of T-cell receptor (TCR) gene rearrangement, positive selection, negative selection, and expression of extracellular membrane markers and co-stimulatory molecules occurs. Pro-T cells arrive at the thymus as "double negative" cells – indicating that they lack both CD4 and CD8 antigens and begin their differentiation in the subcapsular zone. Next, the process of TCR beta gene rearrangement occurs with simultaneous expression of both CD4 and CD8. Once in thymic cortex, the alpha genes rearrange to produce a functional alpha-beta TCR. Subsequently, the processes of positive and negative selection occur with cells that fail either of these tests being eliminated by apoptosis.

Positive selection is the process by which only T cells expressing a TCR that is able to bind self MHC are allowed to survive. Those cells expressing a TCR that is not specific for self MHC are signaled for elimination by apoptosis. This process occurs after TCR DNA rearrangement and prior to the process of negative selection. It occurs in the thymic cortex and involves interaction of T cells with **thymic cortical epithelial cells** expressing self MHC **(Choice D)**. Positive selection is responsible for development of a T cell repertoire that can recognize self.

Negative selection occurs after positive selection and is the process by which T cells possessing TCRs that bind with high affinity to self antigen or self MHC class I or II are eliminated by apoptosis. Negative selection occurs in the thymic medulla and involves interaction of the developing T cells with **thymic medullary epithelial and dendritic cells**. This process serves to eliminate T cells that may be overly autoreactive against self antigens and therefore may play a role in autoimmunity if not destroyed. This results in a population of T cells that have only an appropriately low affinity for self MHC molecules.

(Choice A) Affinity maturation is the process of enhancing the hypervariable region antigen binding affinity that occurs after initial binding of antigen to membrane-bound immunoglobulin on a naïve B lymphocyte and subsequent migration of that B-lymphocyte to a lymph node. Within the germinal center of the lymph node, affinity maturation is accomplished by the process of somatic hypermutation where the DNA coding for the immunoglobulin variable region is mutated randomly at a very high rate. This process results in new immunoglobulins with similar, better, or worse affinity for the antigen; only B cells expressing antibody with enhanced affinity for antigen will be selected for. This process does not occur in T-lymphocyte maturation.

(Choice B) Isotype switching is a process that occurs in naïve B-lymphocytes upon initial exposure to antigen; this process does not occur in T-lymphocyte maturation.

(Choice E) TCR DNA rearrangement is an exceedingly complex process that results in excess of 10^{15} different possible antigen binding sites

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(Choice E) TCR DNA rearrangement is an exceedingly complex process that results in excess of 10^{15} different possible antigen binding sites. The process is similar to that of immunoglobulin gene rearrangement in that it involves joining of V, D, J and C regions of the TCR gene and the processes of junctional flexibility, N and P-region nucleotide addition, alternative joining of genes, and multiple peptides combining to form the intact receptor. The mature TCR is formed from joining of an a and a b protein segment, and these proteins are membrane-bound in close association with either CD4 or CD8 as well as the costimulatory CD28 and CD45.

Educational Objective:
The process of negative selection in T cell maturation is essential for eliminating T cells that bind to self MHC or self antigens with overly high affinity. This process occurs in the thymic medulla. If these cells were permitted to survive, they would likely induce immune and inflammatory reactions against self antigens leading to autoimmune disease.

References

- The thymus and central tolerance.
- Overview of the immune response.

Immunology	Allergy & Immunology	Cell mediated immunity
Subject	System	Topic

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A 38-year-old woman comes to the office due to abdominal pain. For the last 2-3 weeks, she has had increasingly severe abdominal pain associated with watery diarrhea. The patient has a history of Crohn disease treated for the last year with adalimumab, which has controlled the symptoms until now. Vital signs are normal except for a temperature of 37.8 C (100 F). Examination shows moderate tenderness in the right lower quadrant with no peritoneal signs. Laboratory results show an undetectable trough adalimumab level. Which of the following is the most likely explanation for this patient's worsening symptoms?

- A. Development of antidrug antibodies
- B. Formation of insoluble complexes at the injection site
- C. Increased enterohepatic drug recirculation
- D. Increased renal drug elimination
- E. Induction of cytochrome P-450 enzymes

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- ✓ A. Development of antidrug antibodies (55%)
- B. Formation of insoluble complexes at the injection site (13%)
- C. Increased enterohepatic drug recirculation (6%)
- D. Increased renal drug elimination (9%)
- E. Induction of cytochrome P-450 enzymes (14%)

Omitted
Correct answer
A

55%
Answered correctly

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02/01/2020
Last Updated

Explanation

This patient with Crohn disease initially responded to treatment with adalimumab but subsequently experienced treatment failure with a relapse of symptoms after nearly a year of therapy. **Adalimumab** is a recombinant human IgG that binds **tumor necrosis factor-alpha** (TNF-alpha), an inflammatory cytokine involved in promoting leukocyte migration, neutrophil and macrophage function, and granuloma integrity. Adalimumab prevents TNF-alpha from associating with its cell-surface receptors, blocking its pro-inflammatory effects. TNF-alpha inhibitors are used for a variety of inflammatory disorders such as Crohn disease, psoriasis, and rheumatoid arthritis.

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Omitted
Correct answer
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However, use of adalimumab can induce the formation of **antidrug antibodies** (ADAs), which reduce the activity of the agent and lead to more rapid drug clearance and lower trough levels between doses. Patients with ADAs against adalimumab typically experience **declining effectiveness** of treatment and can develop hypersensitivity reactions after administration. The formation of ADAs can also be seen with other immunoglobulin-based anti-TNF agents (eg, infliximab) but is uncommon with etanercept, a recombinant TNF-receptor fusion protein.

(Choice B) Glargine is a long-acting insulin analogue that forms insoluble complexes. This leads to the formation of microprecipitates at the injection site that then slowly dissolve and are released into the circulation throughout the day. Adalimumab is given as a subcutaneous injection but does not form insoluble complexes at the injection site.

(Choice C) Enterohepatic recirculation of certain cancer chemotherapeutic agents (eg, irinotecan) can lead to increased exposure of the intestinal mucosa to the agent and significant gastrointestinal toxicity. However, monoclonal antibodies do not undergo enterohepatic recirculation.

(Choice D) Adalimumab and other therapeutic monoclonal antibodies are eliminated primarily by degradation via receptor-mediated endocytosis in the reticuloendothelial system. Renal elimination of adalimumab can lead to increased drug clearance in patients with protein-losing glomerular disorders but otherwise does not significantly affect pharmacokinetics.

(Choice E) Cytochrome P-450 enzyme inducers (eg, rifampin, carbamazepine, phenobarbital) can cause accelerated clearance of drugs that are metabolized primarily in the liver. Adalimumab does not undergo metabolism by the P-450 system.

Educational objective:
Adalimumab is a recombinant human IgG that binds tumor necrosis factor-alpha (TNF-alpha). Antidrug antibodies can develop against adalimumab (or other immunoglobulin-based anti-TNF agents) that can block its interaction with TNF-alpha, preventing the drug from functioning and leading to more rapid drug clearance.

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References

- The impact of anti-drug antibodies on drug concentrations and clinical outcomes in rheumatoid arthritis patients treated with adalimumab, etanercept, or infliximab: results from a multinational, real-world clinical practice, non-interventional study.

Immunology	Rheumatology/Orthopedics & Sports	Inflammatory bowel disease
Subject	System	Topic

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A 26-year-old man is brought to the emergency department due to fever and lethargy. His girlfriend says the patient abruptly began experiencing fever, chills, vomiting, and diarrhea several hours ago, which were quickly followed by lightheadedness and lethargy. He has no prior medical conditions other than an episode of epistaxis after a bar fight 3 days ago. The patient does not smoke cigarettes or use injection drugs. There is no history of exposure to sick contacts, and he has not eaten anything out of the ordinary. Temperature is 38.9 C (102 F), blood pressure is 90/60 mm Hg, and pulse is 120/min. Physical examination shows a diffuse, erythematous rash. There is an anterior nasal packing in the left nostril, removal of which shows mild mucosal erythema with a purulent discharge. Cardiopulmonary and abdominal examinations reveal no abnormalities, and signs of meningeal irritation are absent. Which of the following processes is most essential in pathogenesis of this patient's current condition?

A. Activation of toll-like receptors by bacterial components

B. Binding of T-cell receptors by bacterial secretory products

C. Bridging of cell-bound IgE by multivalent antigens

D. Phagocytosis of bacteria in the blood by neutrophils

E. Presentation of processed antigens by dendritic cells

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- A. Activation of toll-like receptors by bacterial components (24%)
- ✓ B. Binding of T-cell receptors by bacterial secretory products (55%)
- C. Bridging of cell-bound IgE by multivalent antigens (3%)
- D. Phagocytosis of bacteria in the blood by neutrophils (8%)
- E. Presentation of processed antigens by dendritic cells (6%)

Omitted
Correct answer
B

55%
Answered correctly

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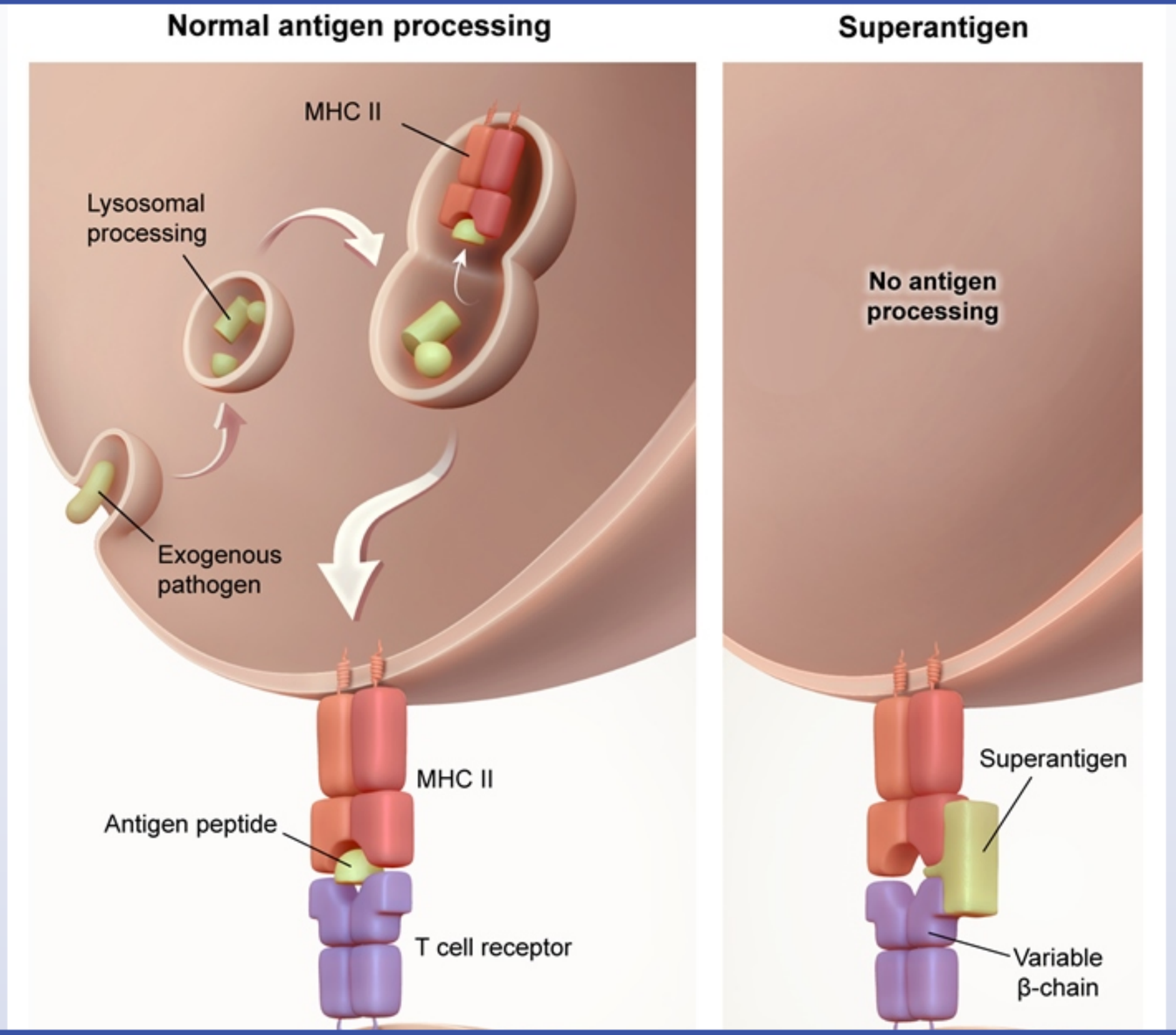
Explanation

Normal antigen processing

Superantigen


Normal antigen processing
MHC II
Lysosomal processing
Exogenous pathogen
MHC II
Antigen peptide
T cell receptor
Superantigen
No antigen processing
Superantigen
Variable β-chain

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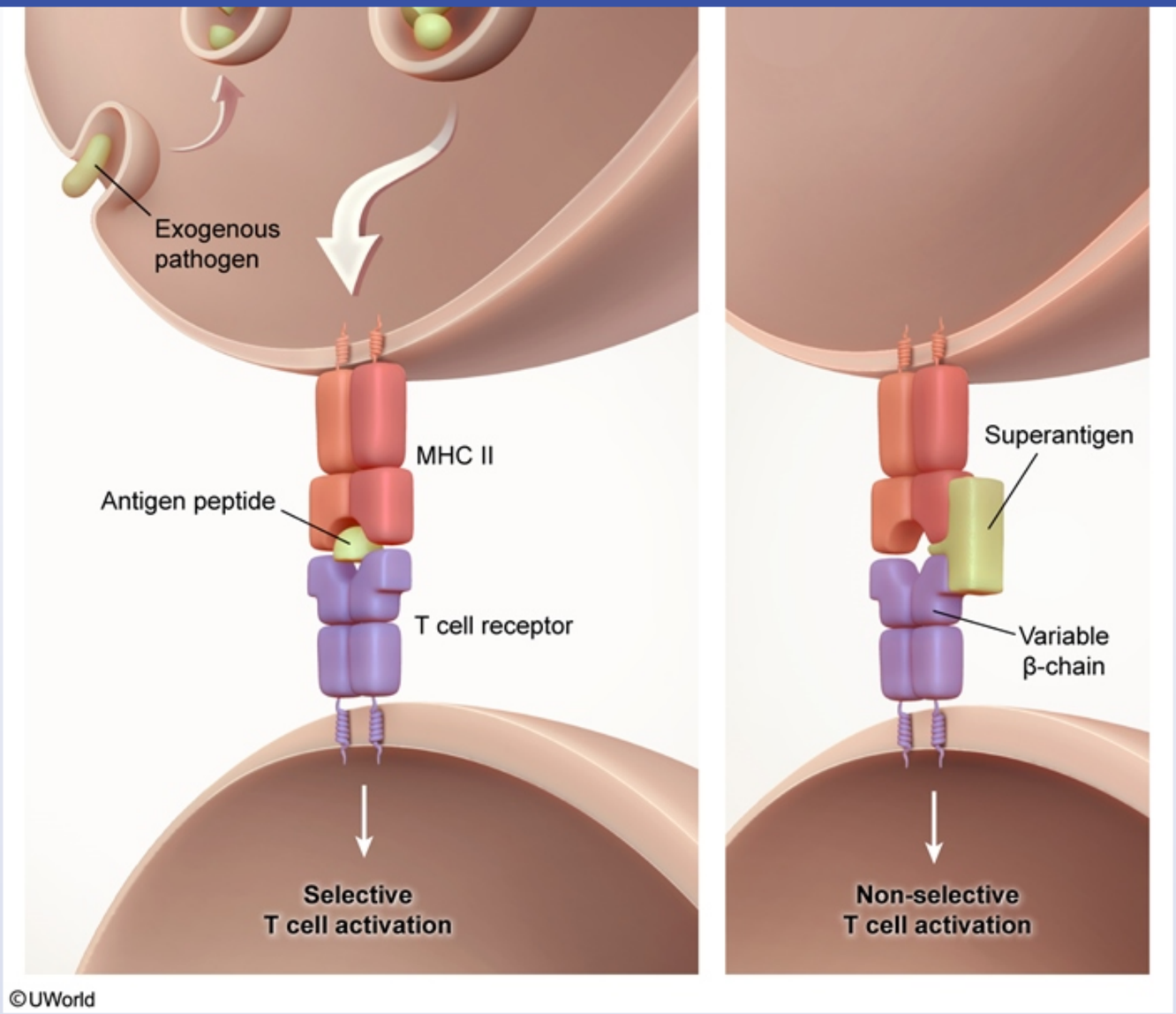

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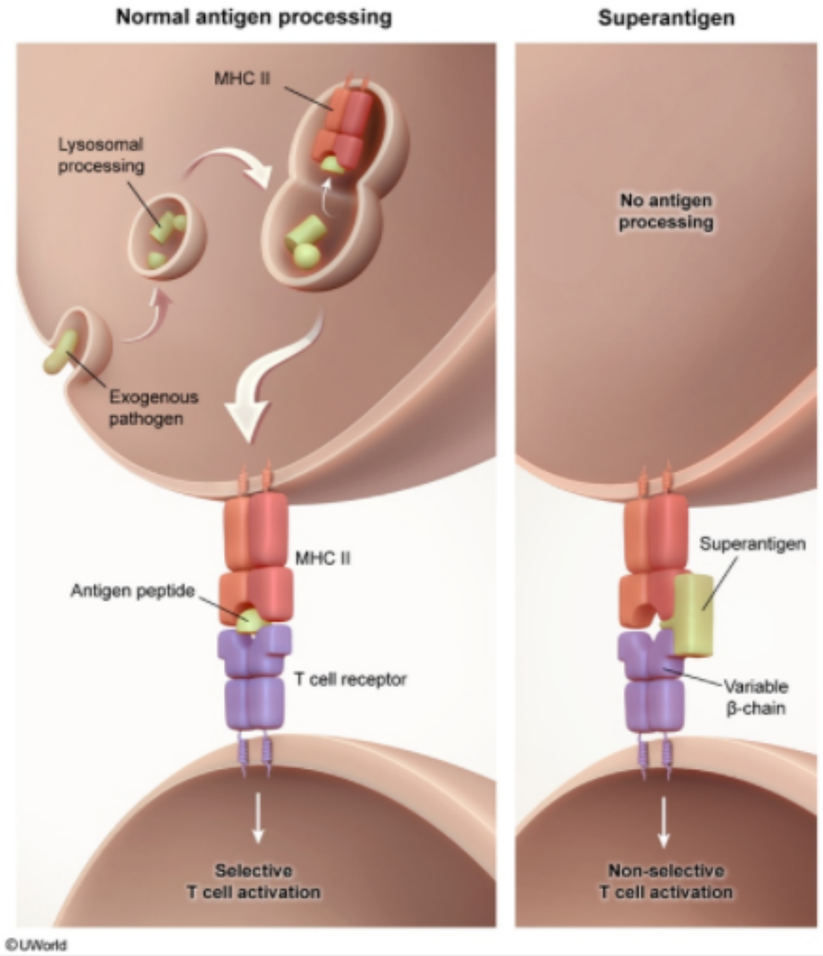

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Staphylococcal toxic shock syndrome (TSS) is an exotoxin-mediated disease associated with rapid-onset high fever, hypotension, multiorgan failure, and a diffuse, erythematous rash. Most cases are linked to prolonged tampon use or **nasal wound packing**, which provides a medium for localized *Staphylococcus aureus* proliferation and the elaboration of **pyrogenic toxin superantigens** (eg, toxic shock syndrome toxin-1 [TSST-1]) into the bloodstream.

Pyrogenic toxin superantigens are generated by strains of *S aureus* (and *Streptococcus pyogenes*) that have acquired an underlying mobile genetic element via bacteriophage or plasmid. These exotoxins are called superantigens because they bind to the invariant region of the MHC-II complex of antigen-presenting cells without first being internalized and processed (MHC-II antigens are normally processed by the phagolysosome) **(Choice E)**. The superantigen/MHC-II complex subsequently interacts with the variable part of the T-cell receptor beta chain, which results in the **nonspecific stimulation** of a large percentage (>20%) of total **T cells** and the massive release of inflammatory cytokines (eg, IL-1, IL-2, TNF-alpha & beta, interferon-gamma). Cytokine release mediates the major manifestations of TSS including fever, increased capillary permeability, and hypotension.

(Choice A) Endotoxin in the cell membrane of gram-negative bacteria can cause rapid-onset fever and hypotension due to activation of toll-like receptors on cells of the innate immune system. However, in this case, the presence of nasal packing and a diffuse, erythematous rash make TSS far more likely than gram-negative sepsis.

(Choice C) Anaphylactic shock occurs due to antigen-stimulated cross-linking of IgE that is bound to basophils or mast cells, which activates the cell and releases massive amounts of inflammatory mediators. Anaphylactic shock is typically characterized by hypotension, bronchospasm, and shortness of breath; most cases are triggered by insect stings, food, or medications, and manifestations occur shortly after exposure.

(Choice D) Patients who develop TSS usually have a noninvasive infection in the vaginal canal or area of wound packing. TSS is mediated by the absorption of superantigens into the blood, not the invasion of bacteria.

Educational objective:
Toxic shock syndrome is typically associated with the prolonged use of tampons or wound packing, which allows *Staphylococcus aureus* to replicate locally and release pyrogenic toxic superantigens (eg, toxic shock syndrome toxin-1) into the blood. Superantigens bind to the MHC-II complex of antigen-presenting cells without processing and nonspecifically activate T cells. This leads to a dramatic release of inflammatory cytokines, which causes the manifestations of the disease (eg, hypotension; high fever; organ failure; diffuse, erythematous rash).

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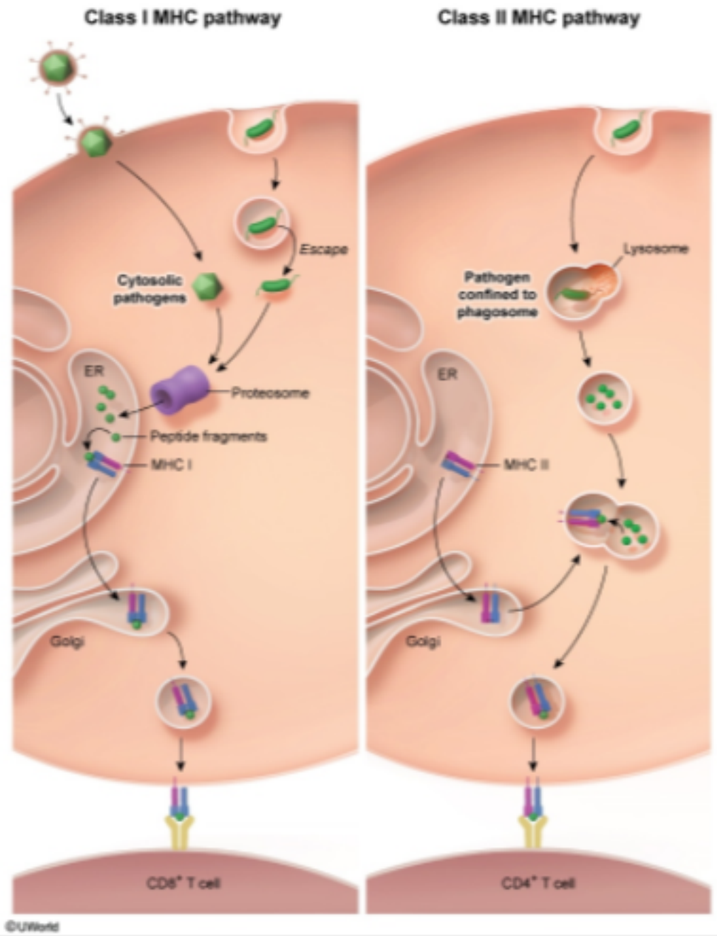

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References

- Exotoxins of Staphylococcus aureus

Immunology	Infectious Diseases	Toxic shock syndrome
Subject	System	Topic

Pyrogenic toxin superantigens are generated by strains of *S aureus* (and *Streptococcus pyogenes*) that have acquired an underlying mobile

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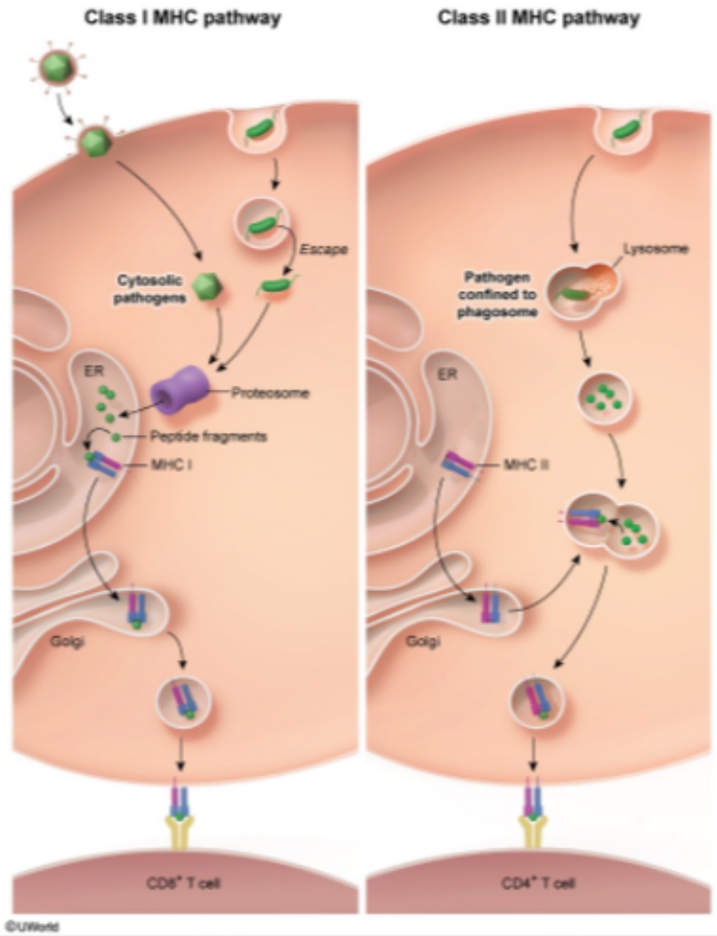

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Subject System Topic

complex of antigen-presenting cells without first being internalized and processed (MHC-II antigens are normally processed by the phagolysosome) **(Choice E)**. The superantigen/MHC-II complex subsequently interacts with the variable part of the T-cell receptor beta chain, which results in the **nonspecific stimulation** of a large percentage (>20%) of total **T cells** and the massive release of inflammatory cytokines (eg, IL-1, IL-2, TNF-alpha & beta, interferon-gamma). Cytokine release mediates the major manifestations of TSS including fever, increased capillary permeability, and hypotension.

(Choice A) Endotoxin in the cell membrane of gram-negative bacteria can cause rapid-onset fever and hypotension due to activation of toll-like receptors on cells of the innate immune system. However, in this case, the presence of nasal packing and a diffuse, erythematous rash make TSS far more likely than gram-negative sepsis.

(Choice C) Anaphylactic shock occurs due to antigen-stimulated cross-linking of IgE that is bound to basophils or mast cells, which activates the cell and releases massive amounts of inflammatory mediators. Anaphylactic shock is typically characterized by hypotension, bronchospasm, and shortness of breath; most cases are triggered by insect stings, food, or medications, and manifestations occur shortly after exposure.

(Choice D) Patients who develop TSS usually have a noninvasive infection in the vaginal canal or area of wound packing. TSS is mediated by the absorption of superantigens into the blood, not the invasion of bacteria.

Educational objective:
Toxic shock syndrome is typically associated with the prolonged use of tampons or wound packing, which allows *Staphylococcus aureus* to replicate locally and release pyrogenic toxic superantigens (eg, toxic shock syndrome toxin-1) into the blood. Superantigens bind to the MHC-II complex of antigen-presenting cells without processing and nonspecifically activate T cells. This leads to a dramatic release of inflammatory cytokines, which causes the manifestations of the disease (eg, hypotension; high fever; organ failure; diffuse, erythematous rash).

References

- Exotoxins of Staphylococcus aureus

Immunology	Infectious Diseases	Toxic shock syndrome
Subject	System	Topic

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An 18-year-old female college student is hospitalized because of high fever, headache, and skin rash. She has had these symptoms for the past 24 hours. She has a history of recurrent infections, including bacterial meningitis 6 months ago that was successfully treated with ceftriaxone. She takes no medication at home. She denies recent travel and insect bites. She does not use tobacco, alcohol, or illicit drugs. Her temperature is 39.1° C (102.4° F), blood pressure is 104/70 mm Hg, and pulse is 110/min and regular. General physical examination reveals a petechial rash on the trunk and extremities, including the palms and soles. Neurologic examination shows lethargy, alertness, fluent speech, and ability to follow commands. She has evidence of neck stiffness and photophobia. Which of the following immune system impairments is the most likely explanation for her symptoms?

- A. Pure T-cell dysfunction
- B. Ineffective intracellular killing
- C. Insufficient IgA production
- D. Inability to form the membrane attack complex

Submit

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- A. Pure T-cell dysfunction (5%)
- B. Ineffective intracellular killing (12%)
- C. Insufficient IgA production (9%)
- ✓ D. Inability to form the membrane attack complex (72%)

Omitted
Correct answer
D

72%
Answered correctly

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Explanation

Patients with deficiencies of the complement factors that form the membrane attack complex (MAC) (i.e., C5b–C9) often experience recurrent infections by *Neisseria* species. The MAC is the end-product of antibody complement fixation. It forms a pore in the bacterial cell membrane, leading to electrolyte disturbances, inflow of free water, and eventual cell lysis. *N. meningitidis* is a common cause of bacterial meningitis, especially in the college dormitory setting. Clinically, *N. meningitidis* presents with high fever, chills, altered mentation, petechial skin rash from

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(Choice A) An example of pure T-cell dysfunction is thymic hypoplasia (i.e., DiGeorge syndrome). DiGeorge syndrome has congenital absence of the thymus and parathyroid glands caused by maldevelopment of the third and fourth pharyngeal pouches. The result is a pure T-cell lymphopenia. The absence of T cells leads to recurrent viral and fungal infections. The absence of parathyroids causes symptomatic hypocalcemia (e.g., tetany).

(Choice B) Chronic granulomatous disease (CGD) is an example of deficient intracellular killing. It is an X-linked immunodeficiency that results from the inability of phagocytes to synthesize NADPH oxidase, an enzyme essential to the lysosomal oxidative burst. Patients with CGD suffer recurrent infections with catalase-positive organisms, such as staphylococci.

(Choice C) Young adults infected with *N. meningitidis* can be at increased risk for disseminated infection if they produce **too much** serum IgA antibody. In these patients, IgA attaches to the bacteria and blocks attachment of the IgM and IgG antibodies that induce complement-mediated bacterial lysis. Unlike IgM and IgG, IgA does not trigger the complement cascade but instead binds to bacteria and prevents them from attaching to mucosal surfaces. Therefore, only IgM and IgG binding can produce a bacteriocidal effect, which is a more effective form of killing bacteria.

Educational objective:
Deficiency of the complement factors that form the membrane attack complex (i.e., C5b-C9) results in recurrent infections by *Neisseria* species.

References

- Recurrent meningococcal meningitis due to partial complement defects and poor anti-meningococcal antibody response.
- Infections of people with complement deficiencies and patients who have undergone splenectomy

Immunology Infectious Diseases Complement deficiency

A 4-year-old boy is brought to the emergency department for difficulty breathing and a productive cough. He has a past medical history of recurrent episodes of sinusitis and otitis media. The respiratory infections typically have a protracted course but respond to high-dose antibiotic therapy. Pulmonary auscultation shows crackles and wheezing. Cardiovascular examination shows a cardiac point of maximal impulse that is palpated at the right 5th intercostal space. Which of the following is most likely to be dysfunctional in this patient?

- A. C1 complement component
- B. Chloride channels
- C. Dynein arms
- D. IL-2 receptors
- E. Immunoglobulin gene rearrangement
- F. NADPH oxidase

Submit

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- A. C1 complement component (2%)
- B. Chloride channels (10%)
- ✓ C. Dynein arms (72%)
- D. IL-2 receptors (2%)
- E. Immunoglobulin gene rearrangement (4%)
- F. NADPH oxidase (7%)

Omitted
Correct answer
C

72%
Answered correctly

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Explanation

Cilium structure

Outer dynein arm

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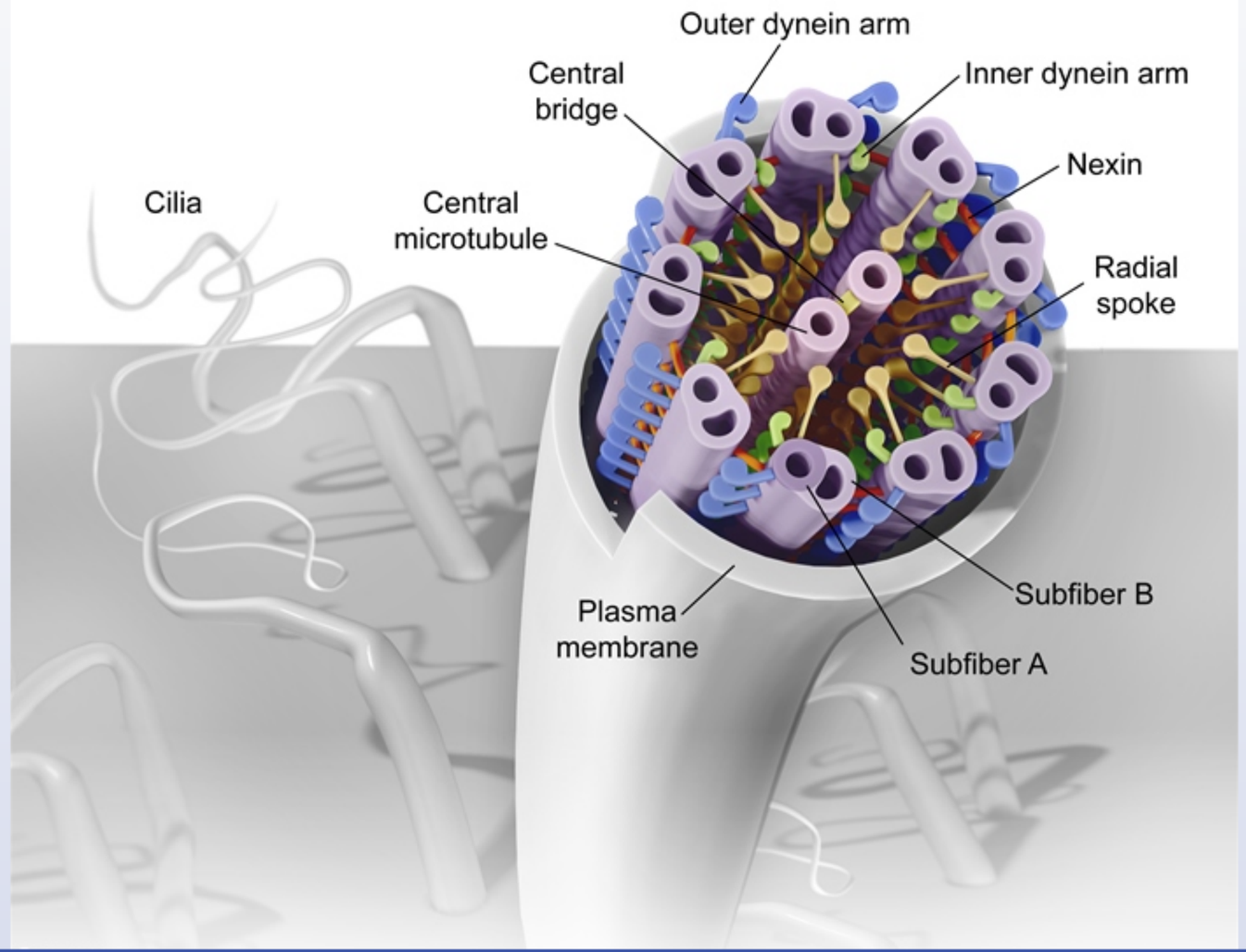
Cilium structure



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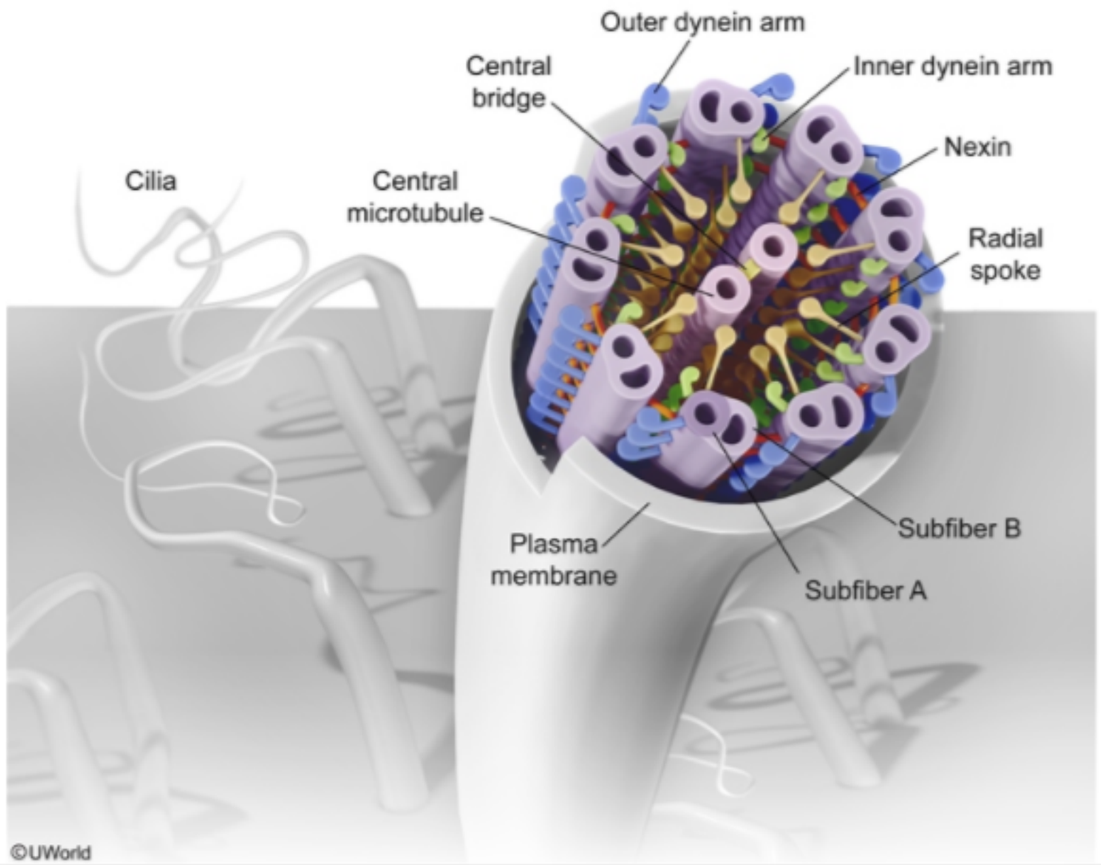
Cilium structure



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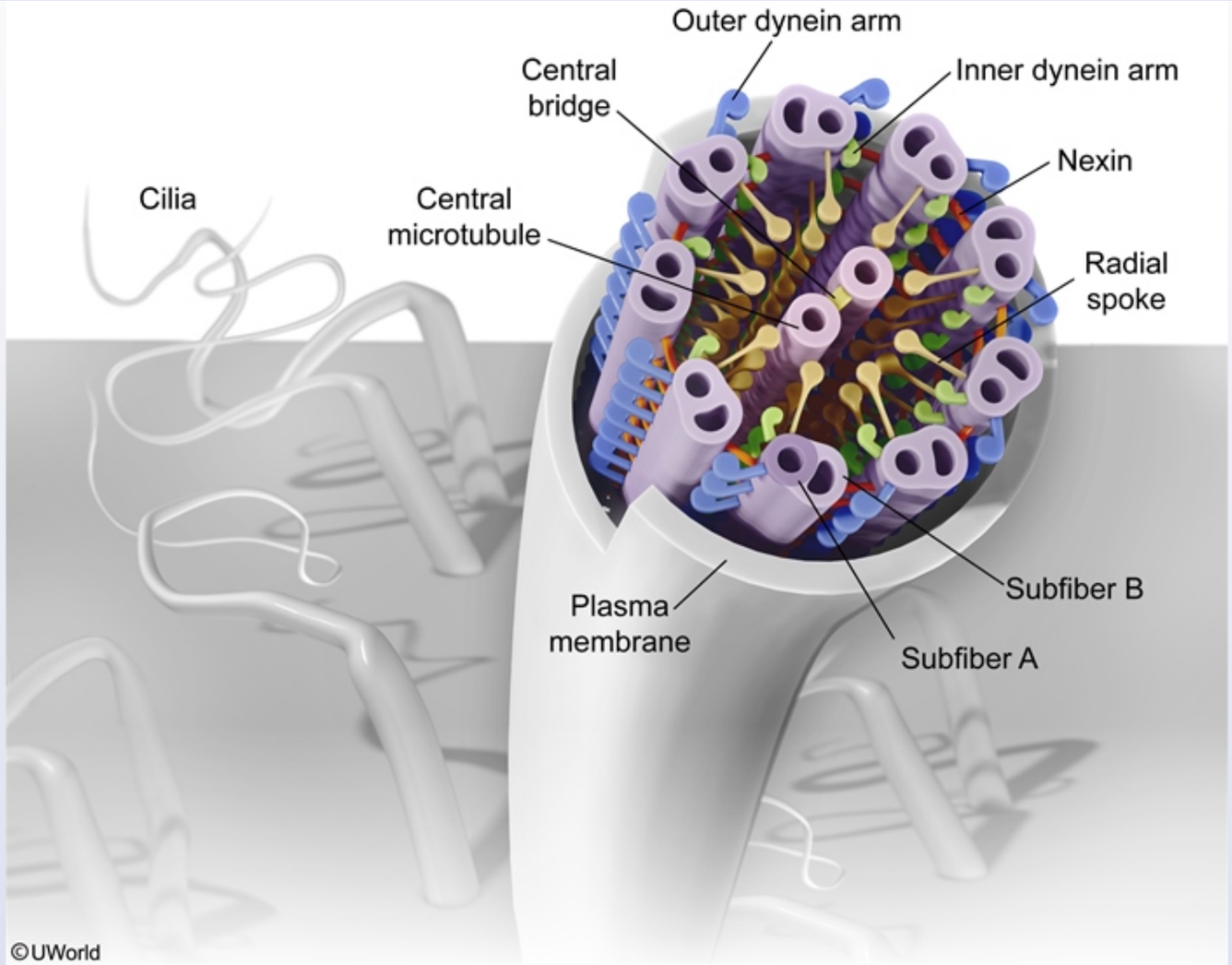

This patient's history of recurrent respiratory infections and dextrocardia on physical examination are suggestive of **Kartagener syndrome**, a form of **primary ciliary dyskinesia** (PCD). This autosomal recessive condition is caused by a wide variety of mutations that impair ciliary structure or function.

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Eukaryotic flagella and cilia are composed of a central core known as the axoneme that is surrounded by cell membrane. The axoneme of flagella and motile cilia consists of a circular array of microtubule doublets surrounding 2 central microtubules (9+2 arrangement); the axoneme is anchored to the cell by a basal body. Each doublet has an A and B subunit and is connected to the adjacent doublet via dynein arms. These dynein arms contain an ATPase that generates energy to slide the microtubules past each other, producing ciliary movement. Primary ciliary dyskinesia can result from failure of the **dynein arms** to develop normally.

Patients with PCD experience **recurrent respiratory infections** (eg, chronic sinusitis, bronchiectasis) as a result of impaired mucociliary clearance. In addition, impaired ciliary movement during embryogenesis can cause **situs inversus** (reversed right/left positioning of internal organs). **Infertility** in men (impaired sperm motility) and women (immobility of fallopian tube cilia) is another frequent manifestation.

(Choice A) Deficiency of the C1 complement component causes increased susceptibility to encapsulated bacteria (eg, *Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis*) and also predisposes to developing systemic lupus erythematosus.

(Choice B) Epithelial cell chloride channels are defective in cystic fibrosis. Although patients with cystic fibrosis typically have recurrent respiratory infections and infertility, dextrocardia/situs inversus are not seen.

(Choice D) Defects in T-cell IL-2 receptors can cause severe combined immunodeficiency disease (SCID).

(Choice E) Immunoglobulin gene rearrangement is impaired in hyper-IgM syndrome. In this disorder, B cells produce high amounts of IgM but are unable to switch production to other immunoglobulin classes.

(Choice F) NADPH oxidase deficiency causes chronic granulomatous disease.

Educational objective:
Kartagener syndrome is a form of primary ciliary dyskinesia characterized by the triad of situs inversus, chronic sinusitis, and bronchiectasis. It occurs due to mutations that impair the structure or function of cilia. Cystic fibrosis also causes chronic respiratory infections, but it is not associated with situs inversus.

This patient's history of recurrent respiratory infections and dextrocardia on physical examination are suggestive of **Kartagener syndrome**, a form

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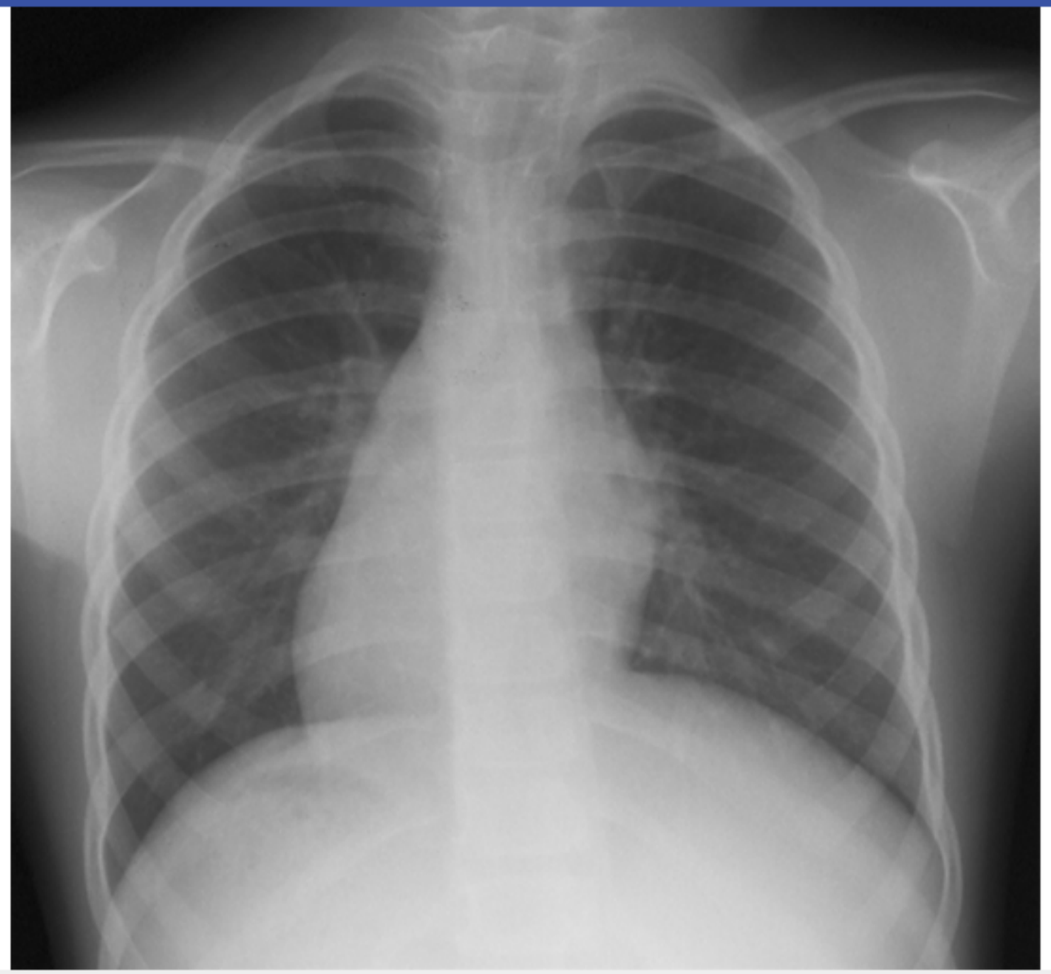

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Immunology	Pulmonary & Critical Care	Immotile cilia syndrome
Subject	System	Topic

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A 45-year-old woman comes to the office due to a long history of joint pain, swelling, and stiffness. She recently immigrated to the United States and had little access to medical care in her original country. On physical examination, her proximal interphalangeal and metacarpophalangeal joints are tender and swollen bilaterally, and her fingers appear significantly deformed. Subcutaneous nodules are palpated near the elbow. Laboratory studies are obtained to confirm the diagnosis. This patient's serum is most likely to contain IgM antibodies against which of the following substances?

- A. Centromeres
- B. Double-stranded DNA
- C. Fc portion of human IgG
- D. Mitochondrial extract
- E. Nuclear basic proteins
- F. Phospholipids
- G. Sheep erythrocytes

Submit

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- A. Centromeres (7%)
- B. Double-stranded DNA (8%)
- ✓ C. Fc portion of human IgG (67%)
- D. Mitochondrial extract (2%)
- E. Nuclear basic proteins (7%)
- F. Phospholipids (4%)
- G. Sheep erythrocytes (1%)

Omitted
Correct answer
C

67%
Answered correctly

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01/15/2020
Last Updated

Explanation

Clinical features of rheumatoid arthritis

Clinical features of rheumatoid arthritis	
Clinical presentation	• Pain, swelling & morning stiffness in multiple joints • **Small joints** (PIP, MCP, MTP); spares DIP joints • Systemic symptoms (fever, weight loss, anemia) • **Cervical spine** involvement: subluxation, cord compression
Laboratory/imaging studies	• Positive rheumatoid factor & **anti-CCP antibodies** • C-reactive protein & ESR correlate with disease activity • **X-ray**: soft tissue swelling, joint space narrowing, bony erosions

Anti-CCP = anti–cyclic citrullinated peptide; **DIP** = distal interphalangeal; **ESR** = erythrocyte sedimentation rate; **MCP** = metacarpophalangeal; **MTP** = metatarsophalangeal; **PIP** = proximal interphalangeal.

Bilateral pain, stiffness, and deformity of the proximal interphalangeal and metacarpophalangeal joints are typical of advanced **rheumatoid arthritis** (RA). Morning stiffness, tenderness, and edema of the affected joints predominate early in this disease. Later, osteopenia, erosions, and joint space narrowing lead to decreased range of motion and deformities (eg, swan neck, ulnar deviation). Patients can also develop rheumatoid nodules, firm, nontender, subcutaneous nodules that occur at pressure points such as the elbows or forearms.

RA is due to failure of immune tolerance, with development of an autoreactive immune response directed against joint components (eg, type II collagen, citrullinated vimentin). $CD4^+$ T-helper cells become activated by these self-antigens and release cytokines that promote chronic inflammatory synovitis. $CD4^+$ T cells also induce B cells to synthesize **rheumatoid factor** and anti-citrullinated protein antibodies (ACPAs). Rheumatoid factor is an antibody (typically IgM) specific for the **Fc component of IgG**. Rheumatoid factor binds circulating IgG and ACPAs bind modified self-proteins, forming immune complexes that deposit on the synovium and cartilage. These complexes activate complement in those locations, contributing to chronic inflammation and joint destruction.

(Choice A) Anticentromere antibodies are found in the majority of patients with CREST syndrome.

(Choice B) Antibodies to double-stranded DNA (anti-dsDNA) are specific for systemic lupus erythematosus.

(Choice D) Antimitochondrial antibodies are found in patients with primary biliary cholangitis.

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(Choice B) Antibodies to double-stranded DNA (anti-dsDNA) are specific for systemic lupus erythematosus.

(Choice D) Antimitochondrial antibodies are found in patients with primary biliary cholangitis.

(Choice E) The presence of antinuclear antibodies is a nonspecific finding in many connective tissue disorders. These can occur in IgM form, but would be found less frequently than rheumatoid factor in patients with RA.

(Choice F) Antiphospholipid antibodies can be found in patients with systemic lupus erythematosus and antiphospholipid antibody syndrome. Antiphospholipid antibodies cause a hypercoagulable state with paradoxical PTT prolongation.

(Choice G) The Monospot test assesses the serum's ability to agglutinate sheep erythrocytes. It is positive in the presence of heterophile antibodies and is used to diagnose infectious mononucleosis due to Epstein-Barr virus.

Educational objective:
Rheumatoid arthritis results from an immune response directed against autoantigens in the joints. Infiltrating CD4⁺ T cells secrete cytokines that promote inflammatory synovitis. They also stimulate B cells to produce rheumatoid factor (IgM antibody specific for Fc component of IgG) and anti-citrullinated protein antibodies that contribute to chronic inflammation and joint destruction.

Immunology	Rheumatology/Orthopedics & Sports	Rheumatoid arthritis
Subject	System	Topic

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- Pain, swelling & morning stiffness in multiple joints

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(Choice E) The presence of antinuclear antibodies is a nonspecific finding in many connective tissue disorders. These can occur in IgM form, but

Clinical presentation	• Pain, swelling & morning stiffness in multiple joints • **Small joints** (PIP, MCP, MTP); s • Systemic symptoms (fever, weig • **Cervical spine** involvement: sub
Laboratory/imaging studies	• Positive rheumatoid factor & **ant** • C-reactive protein & ESR correla • **X-ray**: soft tissue swelling, joint s

Anti-CCP = anti–cyclic citrullinated peptide; **DIP** = distal interphalangeal; **ESR** = erythro
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Bilateral pain, stiffness, and deformity of the proximal interphalangeal and metacarpophalangeal joints are typical of advanced **rheumatoid**

Exhibit Display

CREST syndrome characteristics
Calcinosis
Raynaud phenomenon
Esophageal dysmotility
Sclerodactyly
Telangiectasias

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anti-citrullinated protein antibodies that contribute to chronic inflammation and joint destruction.

A 22-year-old woman comes to the office due to 2 weeks of profound fatigue, which has prevented her from attending college classes. The fatigue was preceded by fevers and sore throat, but these have now improved. The patient is an exchange student from Turkey and has no prior medical conditions. She does not use tobacco, alcohol, or illicit drugs. Vital signs are within normal limits. Oropharyngeal examination shows no abnormalities. There are several enlarged lymph nodes posterior to the sternocleidomastoid muscle bilaterally. Cardiopulmonary examination is unremarkable. The spleen is palpable 1 cm below the left costal margin. No skin rashes or other lymphadenopathy is present. Peripheral blood evaluation shows increased numbers of abnormal white blood cells as shown in the exhibit. The observed cytoplasmic granules of these cells are most likely to contain which of the following substances?

- A. Elastase
- B. Immunoglobulins
- C. Major basic protein
- D. Perforin
- E. Ribosomes
- F. Viral capsid

Submit

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- A. Elastase (2%)
- B. Immunoglobulins (16%)
- C. Major basic protein (13%)
- ✓ D. Perforin (37%)
- E. Ribosomes (6%)
- F. Viral capsid (22%)

Omitted
Correct answer
D

37%
Answered correctly

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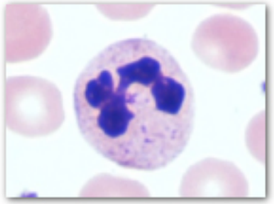
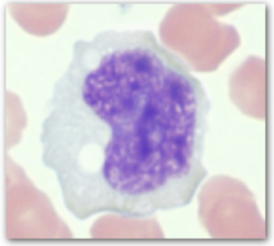
Explanation

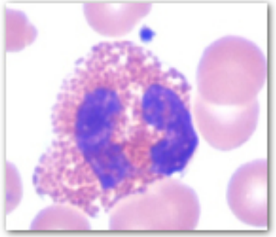
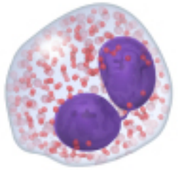
Leukocytes in peripheral blood



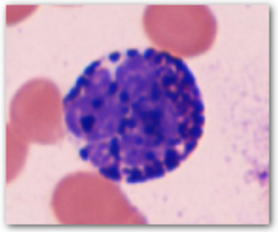
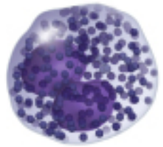
Neutrophil
- Nucleus with 2-5 lobes joined by thin strand
- Pinkish cytoplasm



Monocyte
- Large nucleus, often with a notch
- Grayish vacuolated cytoplasm

Eosinophil
- Bilobed nucleus
- Reddish-orange granular cytoplasm

Basophil
- Coarse, dense blue-black granules

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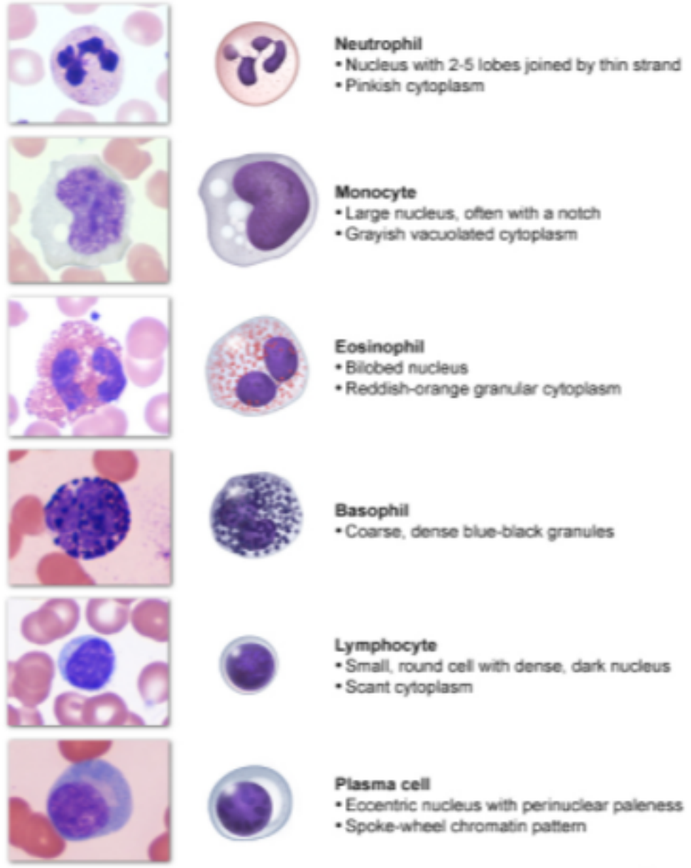
Leukocytes in peripheral blood



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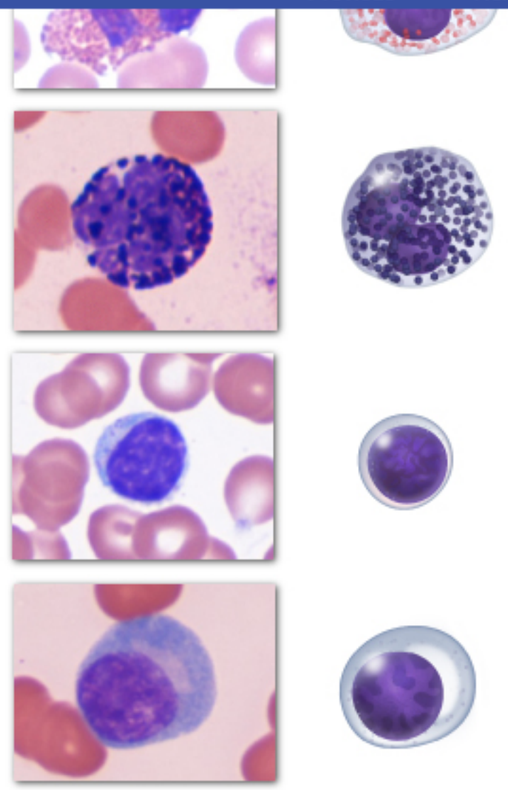

• Reddish-orange granular cytoplasm

Basophil
• Coarse, dense blue-black granules

Lymphocyte
• Small, round cell with dense, dark nucleus
• Scant cytoplasm

Plasma cell
• Eccentric nucleus with perinuclear paleness
• Spoke-wheel chromatin pattern

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This patient's peripheral blood smear reveals a reactive (atypical) lymphocyte. In contrast to normal lymphocytes, which are small, round, and have minimal cytoplasm, reactive lymphocytes are large, **scalloped**, and have abundant cytoplasm.

Reactive lymphocytes are activated, pathogen-specific **cytotoxic T cells** and natural killer cells that form in response to certain **intracellular infections** (eg, HIV, cytomegalovirus, toxoplasmosis); they are particularly linked to **infectious mononucleosis**, a primary Epstein-Barr virus characterized by fever, pharyngitis, adenopathy, splenomegaly, and severe fatigue (as is likely in this patient).

Reactive lymphocytes are effector cells that contain **cytotoxic granules** composed of **perforin** (creates holes in the infected cell's membrane) and granzymes (enter the cytoplasm of infected cells and trigger cell death), which are released in response to foreign antigens on the surface

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Reactive lymphocytes are effector cells that contain **cytotoxic granules** composed of **perforin** (creates holes in the infected cell's membrane) and granzymes (enter the cytoplasm of infected cells and trigger cell death), which are released in response to foreign antigens on the surface (MHC class I receptors) of infected host cells.

(Choice A) Elastase breaks down collagen and is released by neutrophils and macrophages during acute inflammation. Neutrophils have multi-lobe nuclei and pinkish cytoplasm; macrophages have central round nuclei and abundant greyish, vacuolated cytoplasm. Neither typically has scalloped edges or abundant basophilic cytoplasm.

(Choice B) Immunoglobulins are secreted by plasma cells, which have an eccentric nucleus, perinuclear paleness (large Golgi apparatus), and spoke-wheel chromatin. Although immunoglobins cannot typically be visualized on light microscopy, immunoglobulin inclusions can sometimes be seen in plasma cell malignancies such as multiple myeloma (characterized by anemia, hypercalcemia, bone pain, and renal insufficiency).

(Choice C) Eosinophils generate and release major basic protein, which is the core constituent of eosinophilic granules; it acts as a cytotoxin and helminthotoxin and mediates epithelial damage, exfoliation, and bronchospasm in hypersensitivity diseases. Eosinophils have a bilobed nucleus and stain intensely pink.

(Choice E) Ribosomes generate proteins from messenger RNA; they can be visualized by electron microscopy but usually cannot be seen on light microscopy. However, ribosomal aggregates can sometimes be seen as basophilic stippling in patients with thalassemia or alcoholism.

(Choice F) Viral capsids are usually bound to viral genomes and shed in the cytoplasm prior to viral replication. This typically cannot be seen on light microscopy. Atypical lymphocytes are not infected by virus; they react to infected cells.

Educational objective:
Reactive (atypical) lymphocytes are activated, pathogen-specific cytotoxic T cells or natural killer cells that form in response to certain intracellular

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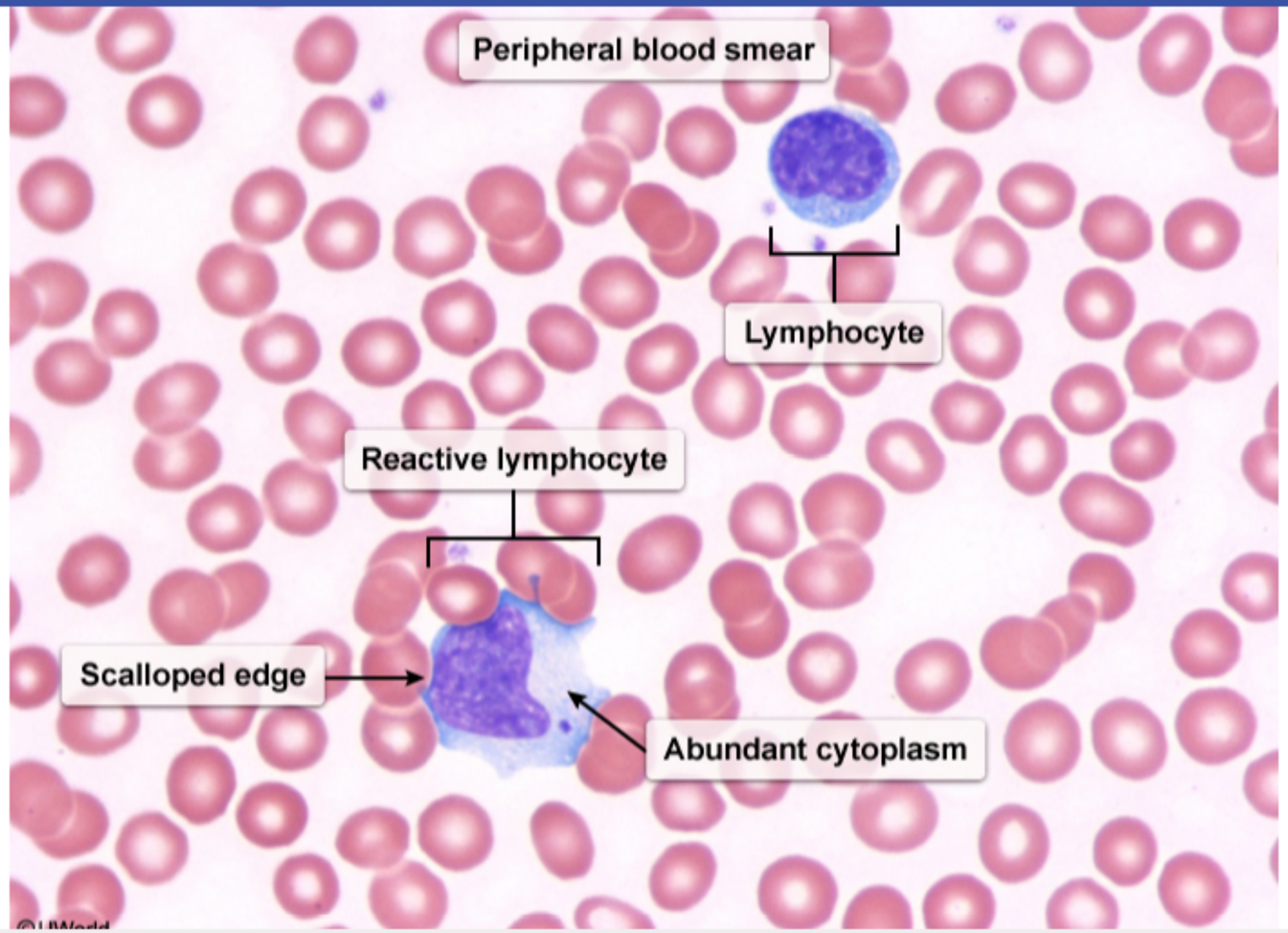

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Educational objective:
Reactive (atypical) lymphocytes are activated, pathogen-specific cytotoxic T cells or natural killer cells that form in response to certain intracellular infections. In contrast to normal lymphocytes, reactive lymphocytes are large, scalloped, and have abundant cytoplasm. Reactive lymphocytosis is a diagnostic feature of infectious mononucleosis.

Immunology	Infectious Diseases	Infectious mononucleosis
Subject	System	Topic

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A 7-year-old boy is evaluated for a foot wound. He sustained a splinter injury to his left foot while playing in the yard several days ago and has continued to have purulent drainage from the wound. The patient has no significant medical history and is up to date with all recommended vaccinations. Wound examination reveals a small retained foreign body with surrounding necrotic tissue and pus. Anaerobic culture of the wound swab grows thin, gram-positive rods with terminal spore, which is biochemically identified as *Clostridium tetani*. Which of the following most likely protected this patient from developing neurological symptoms of the infection?

- A. Activated macrophages capable of killing the bacteria
- B. Circulating antibodies that activate complement
- C. Circulating antibodies that neutralize bacterial products
- D. Neutrophil infiltration of the wound with lysosomal enzyme release
- E. Sensitized $CD8^+$ lymphocytes capable of killing the bacteria

Submit

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- A. Activated macrophages capable of killing the bacteria (3%)
- B. Circulating antibodies that activate complement (11%)
- ✓ C. Circulating antibodies that neutralize bacterial products (68%)
- D. Neutrophil infiltration of the wound with lysosomal enzyme release (8%)
- E. Sensitized $CD8^+$ lymphocytes capable of killing the bacteria (8%)

Omitted
Correct answer
C

68%
Answered correctly

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Last Updated

Explanation

Clostridium tetani is a thin, gram-positive rod with a round terminal spore that grows in strict anaerobic conditions. It is a normal commensal of the gastrointestinal tract of many mammals and is found in soil worldwide. Transmission to humans typically occurs when *C tetani* spores are inoculated into a **skin wound**. In anaerobic conditions, the spores germinate into a vegetative rod and replicate locally. The bacteria also produce an neurotoxic exotoxin called **tetanospasmin** (tetanus toxin) that travels by retrograde axonal transport through the lower motor neurons to the central nervous system. Here, it acts at the level of the anterior horn cells, **blocking inhibitory neurotransmission**, which results in the clinical

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In the United States, the **tetanus toxoid vaccine** (formaldehyde-inactivated tetanus toxin) is part of routine childhood vaccinations. This vaccine stimulates a **humoral antibody response** against tetanus toxoid that prevents the toxoid from causing neurological damage. Tetanus is very rare in those who have been vaccinated; almost all cases occur in unvaccinated individuals or those who have not received appropriate booster vaccines.

(Choice A) Activated macrophages engulf and digest foreign microbes and are the principal cell type responsible for granuloma formation. Although macrophages help clear bacteria locally from the wound, they would not be able to neutralize the tetanus toxin secreted by *Clostridium tetani*.

(Choice B) Circulating antibodies bind to extracellular pathogens and promote complement fixation and phagocytosis. Complement can opsonize and/or neutralize extracellular bacteria but would not impair the activity of tetanus toxin.

(Choice D) Neutrophils are responsible for phagocytosis of foreign organisms and are part of the initial response against extracellular pathogens. These cells play a role in nonspecific innate immunity but are not effective in eliminating the tetanus toxoid.

(Choice E) Cytotoxic CD8 lymphocytes play an important role in host defense against viral infections. They are also capable of destroying tumor cells and contribute to rejection reactions.

Educational objective:
Clostridium tetani produces the neurotoxin tetanospasmin, which blocks inhibitory neurotransmission in the spinal cord and leads to tonic muscular contraction. Tetanus is prevented by immunization with an inactivated toxoid that triggers the production of antitoxin antibodies (active immunity).

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Immunology	Infectious Diseases	Tetanus
Subject	System	Topic

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an neurotoxic exotoxin called **tetanospasmin** (tetanus toxin) that travels by retrograde axonal transport through the lower motor neurons to the

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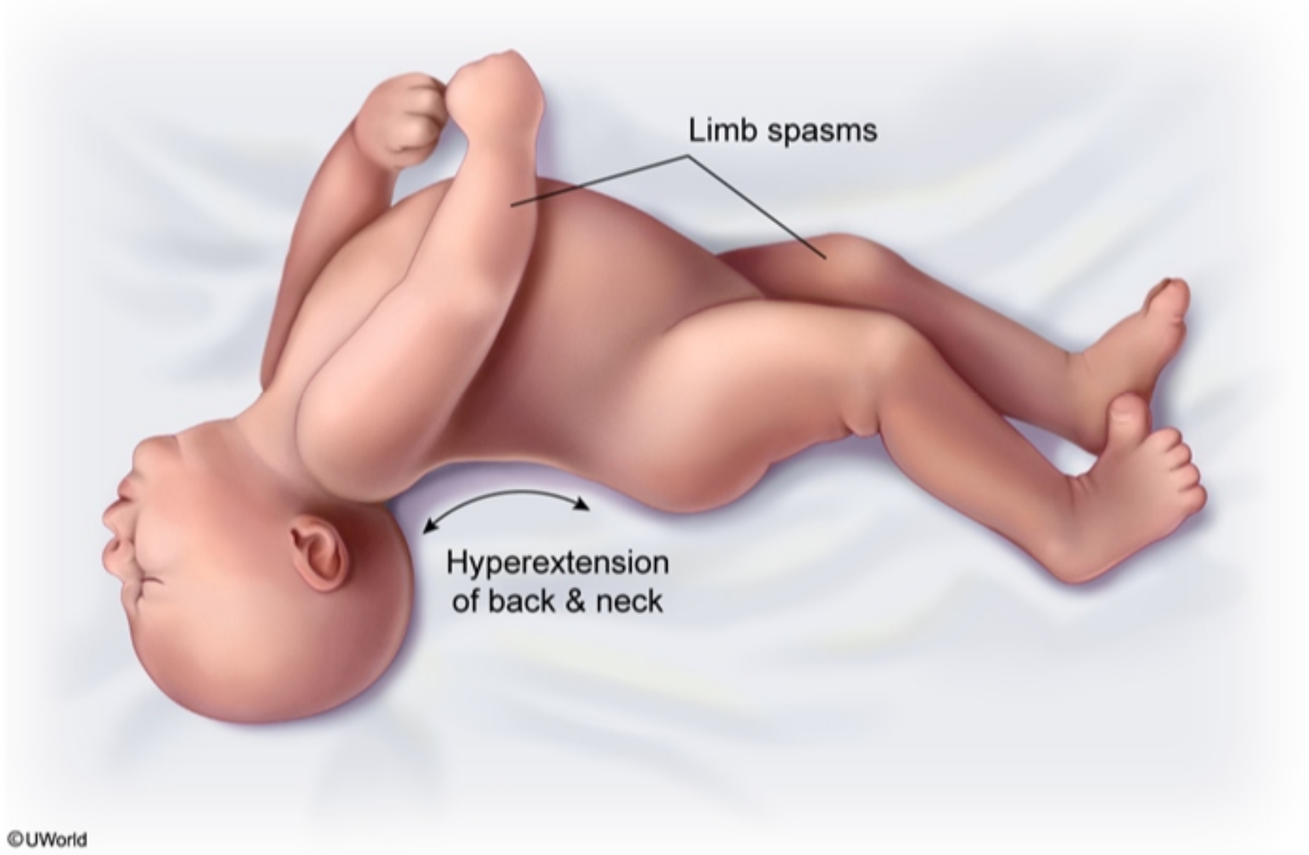
Opisthotonos



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A 55-year-old man with end-stage hepatitis C virus infection undergoes orthotopic liver transplantation from a deceased donor. The patient has no perioperative complications and is discharged from the hospital on appropriate immunosuppressant medications. One week after the surgery, he develops nausea, vomiting, abdominal pain, and bloody diarrhea. Physical examination shows a painful maculopapular rash over his neck, back, and extremities that extends to the palms and soles. Endoscopic evaluation reveals multiple ulcerations of the intestinal mucosa. Which of the following is the most likely cause of this patient's current condition?

A. Graft B cell sensitization against host MHC antigens

B. Graft T cell sensitization against host MHC antigens

C. Host B cell sensitization against graft MHC antigens

D. Host T cell sensitization against graft MHC antigens

E. Preformed antibodies against graft ABO antigens

Submit

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- A. Graft B cell sensitization against host MHC antigens (4%)
- ✓ B. Graft T cell sensitization against host MHC antigens (55%)
- C. Host B cell sensitization against graft MHC antigens (8%)
- D. Host T cell sensitization against graft MHC antigens (29%)
- E. Preformed antibodies against graft ABO antigens (1%)

Omitted
Correct answer
B

55%
Answered correctly

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Explanation

This patient most likely has **graft-versus-host disease** (GVHD), a condition that usually occurs after allogeneic bone marrow transplantation. However, GVHD can also occur following transplantation of organs rich in lymphocytes (eg, **liver**) or transfusion of non-irradiated blood.

Patients affected by GVHD are generally severely immunodeficient due to the primary disease process or as a result of immunosuppressive medications. This allows immunocompetent **donor T cells** from the graft to survive and migrate into host tissues, where they recognize **host**

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Patients affected by GVHD are generally severely immunodeficient due to the primary disease process or as a result of immunosuppressive medications. This allows immunocompetent **donor T cells** from the graft to survive and migrate into host tissues, where they recognize **host MHC antigens** as foreign and become sensitized. On activation, donor $CD4^+$ and $CD8^+$ T cells (not B cells) participate in host cell destruction **(Choice A)**.

Any organ may be a target of GVHD, but the skin, liver, and gastrointestinal (GI) tract are the most frequently affected. Early signs of GVHD include a diffuse maculopapular rash that has a predilection for the palms and soles and may **desquamate** in severe cases. GI tract involvement causes **diarrhea**, intestinal bleeding, and abdominal pain. Liver damage will manifest as abnormal liver function tests. In this case, the donated liver would not be significantly affected as the donor T cells perceive the liver as self.

(Choices C and D) Acute and chronic graft rejections occur following host T and B cell sensitization against graft MHC antigens. The resulting immune response leads to graft failure without significant involvement of other organ systems. This patient's skin and GI findings make GVHD more likely.

(Choice E) If the tissue recipient has antibodies against donor ABO antigens, hyperacute rejection will develop within minutes of transplantation. Spasm and occlusion of graft vessels occur, leading to ischemia and necrosis.

Educational objective:
Graft-versus-host disease can occur following transplantation of organs rich in lymphocytes (eg, liver). T lymphocytes found in the donor organ become sensitized against the MHC antigens of the recipient and subsequently attack the host's tissues. The skin, liver, and gastrointestinal tract are most frequently affected.

Immunology	Dermatology	Graft versus host disease
Subject	System	Topic

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Immunology	Dermatology	Graft versus host disease
Subject	System	Topic

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A 71-year-old man with chronic obstructive pulmonary disease (COPD) is hospitalized due to shortness of breath and wheezing. The patient is treated with bronchodilators and systemic corticosteroids for acute COPD exacerbation. His symptoms improve over the next 2 days. Before being discharged, an intramuscular vaccine containing inactivated viral components, which he normally receives annually, is administered. Several weeks later, the patient comes in close contact with an individual infected with the same virus contained in the vaccine. Which of the following is most likely to occur in this patient as a result of the vaccination?

A. Destruction of infected cells by $CD8^+$ T lymphocytes

B. Impaired intracellular viral assembly

C. Impaired release of viral progeny from cells

D. Inhibition of viral entry into cells

E. Inhibition of viral genome replication

Submit

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- A. Destruction of infected cells by $CD8^+$ T lymphocytes (46%)
- B. Impaired intracellular viral assembly (2%)
- C. Impaired release of viral progeny from cells (7%)
- ✓ D. Inhibition of viral entry into cells (40%)
- E. Inhibition of viral genome replication (3%)

Omitted
Correct answer
D

40%
Answered correctly

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Explanation

Influenza virus life cycle

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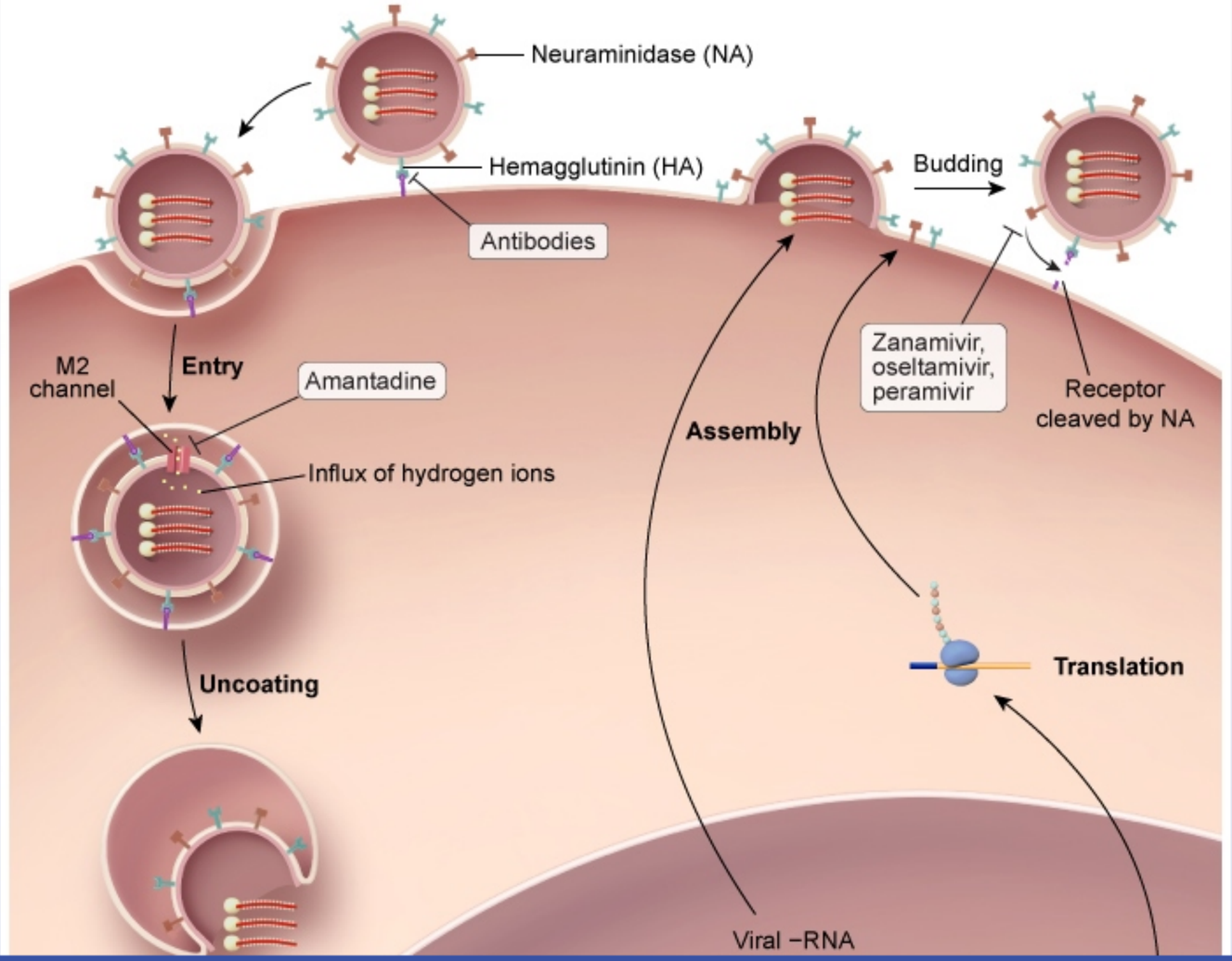
Influenza virus life cycle



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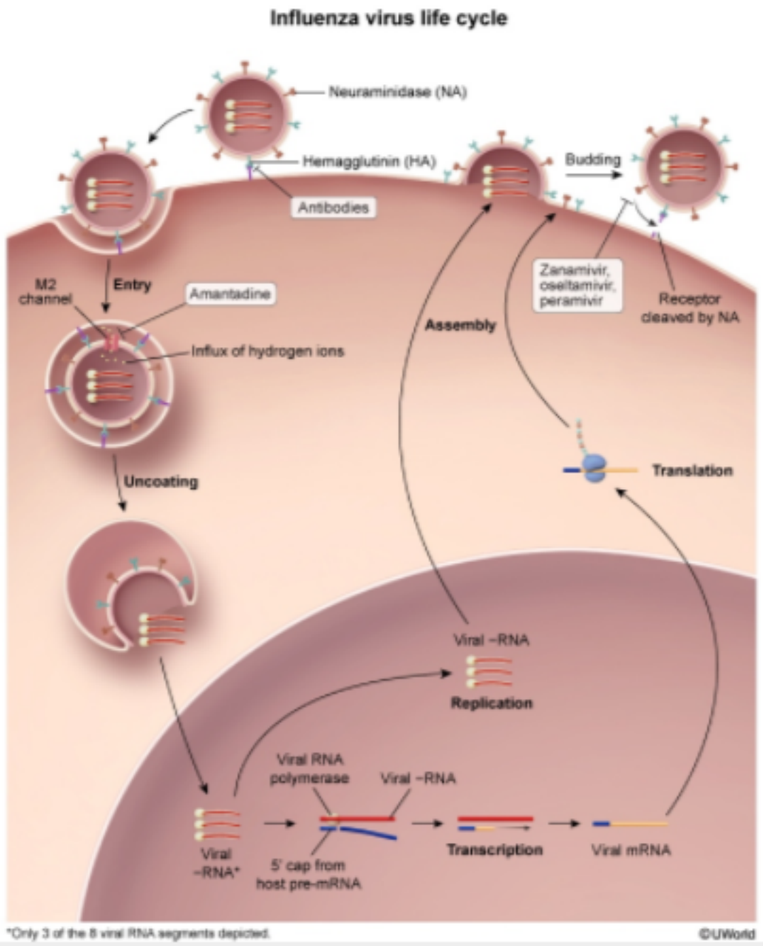

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Viral −RNA

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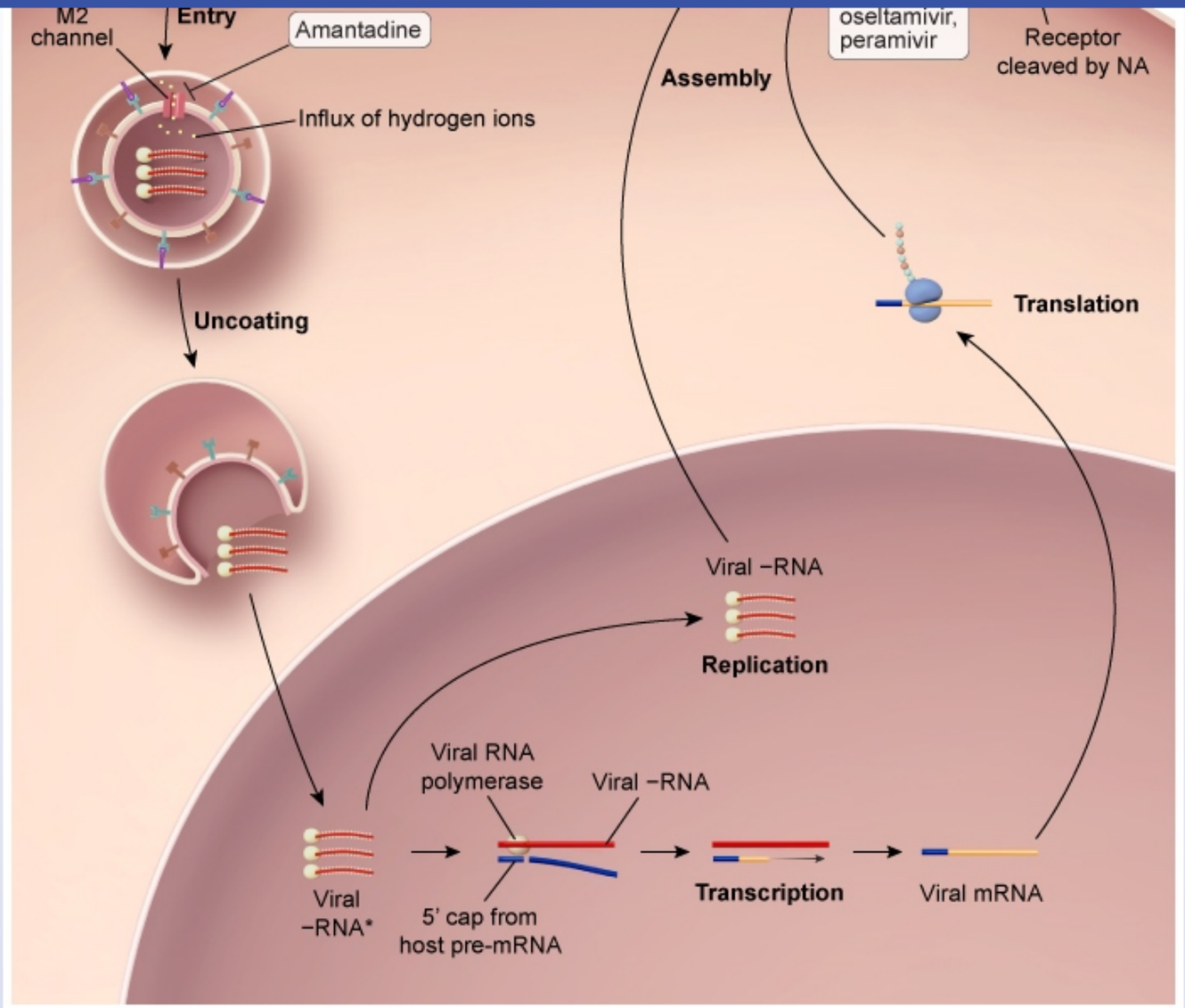

*Only 3 of the 8 viral RNA segments depicted.

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Only 3 of the 8 viral RNA segments depicted.

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Influenza vaccination is administered either by injection (inactivated [killed] vaccine) or nasal spray (live attenuated vaccine). Each seasonal influenza vaccine contains antigens (or attenuated virions) from 3 or 4 influenza A and B virus strains. Antigens from multiple influenza types are included in the vaccine because antibodies against 1 strain confer limited or no protection against the others. **Annual vaccination** is recommended due to waning effectiveness over time and because circulating strains of influenza change from year to year. All individuals age >6 months should be immunized, especially health care workers and those at risk of serious complications such as the elderly, patients with chronic illness (eg, chronic obstructive pulmonary disease), and immunocompromised individuals.

Inactivated versions of the influenza vaccine stimulate the formation of **neutralizing antibodies** against the **hemagglutinin antigen** of included strains. Subsequent exposure to a strain of influenza included in the vaccine will not result in infection because the antibodies bind to hemagglutinin, thereby preventing hemagglutinin from attaching to the sialic acid receptor on host respiratory epithelial cells (**preventing viral entry**).

(Choice A) Because inactivated viral vaccines do not infect host cells, they are not processed by the MHC class I pathway and do not stimulate a potent $CD8^+$ T-cell response. In contrast, live attenuated influenza vaccines replicate in nasopharyngeal cells and are displayed on MHC class I molecules, thereby generating a strong cytotoxic T-cell response that results in the destruction of the infected cell.

(Choices B and E) Protective antibodies against influenza primarily target the surface glycoproteins and impair viral entry. Immunization does not typically affect viral genomic replication or assembly, which occurs in the interior of the cell and cannot be targeted easily by an antibody response.

(Choice C) Neuraminidase cleaves the terminal sialic acid residues on glycoconjugate receptors, which releases influenza virions from infected cells. Oseltamivir is a sialic acid analogue that competitively inhibits influenza neuraminidase, which prevents release of viral progeny.

Educational objective:
Inactivated (killed or component) viral vaccines primarily generate a humoral immune response against extracellular viral antigens, preventing viral entry into the cell. In contrast, live attenuated viral vaccines can generate a strong cell-mediated immune response that can kill virally-infected cells, in addition to providing humoral immunity.

Immunology Infectious Diseases Immunizations

recommended due to waning effectiveness over time and because circulating strains of influenza change from year to year. All individuals age ≥6

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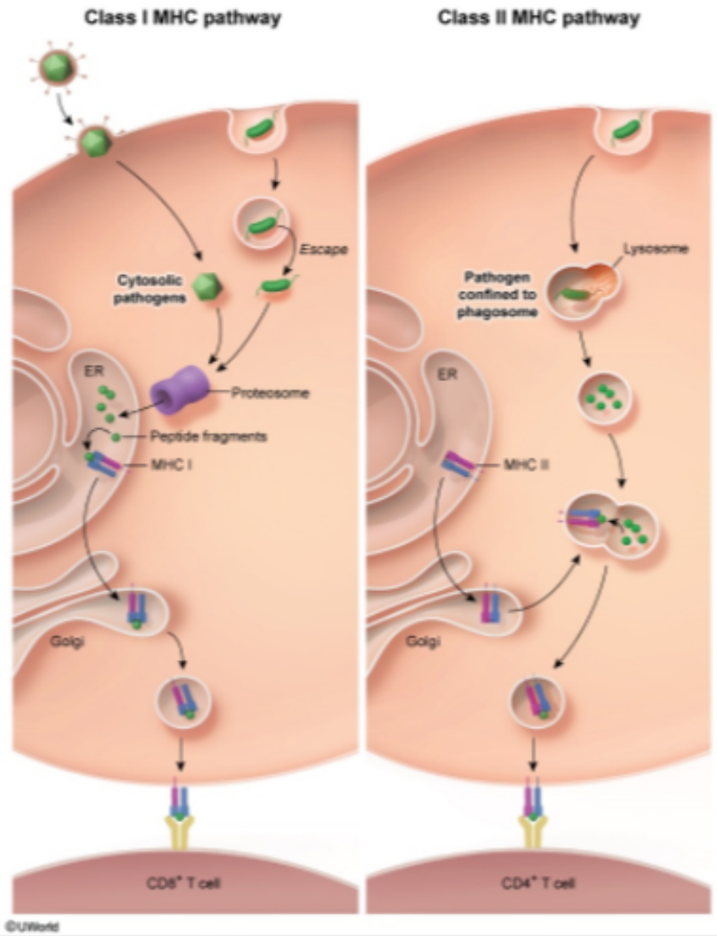

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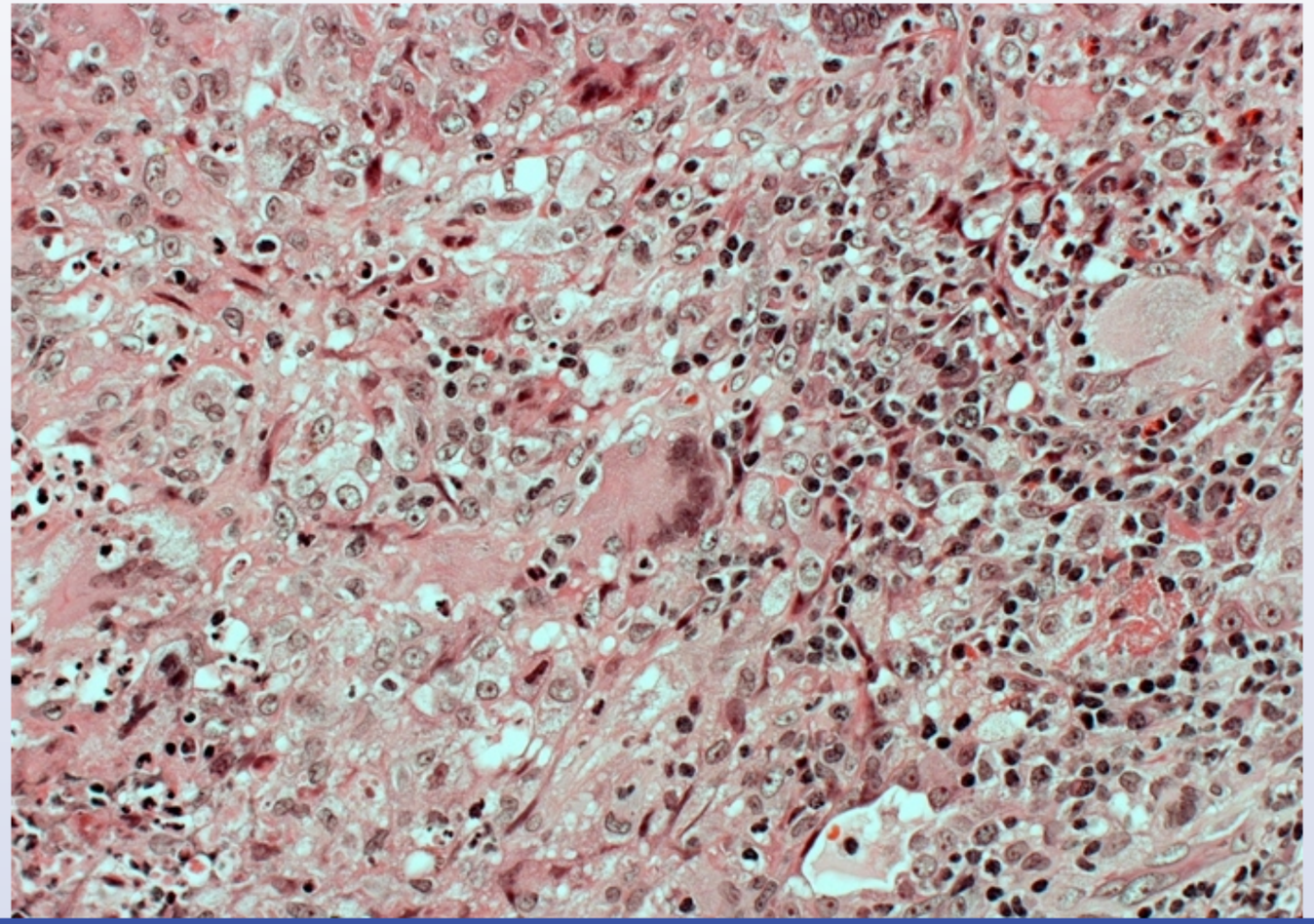
A 64-year-old man comes to the clinic due to several weeks of persistent cough, fever, and weight loss. He smokes a pack of cigarettes daily and drinks 10-12 beers on weekends. Chest x-ray reveals an infiltrate in the left upper lobe. The patient is prescribed broad-spectrum antibiotic therapy for both aspiration and community-acquired pneumonia, but his symptoms worsen despite taking the medication as prescribed. Sputum Gram stain does not reveal any organisms. Lung biopsy findings are shown in the image below:



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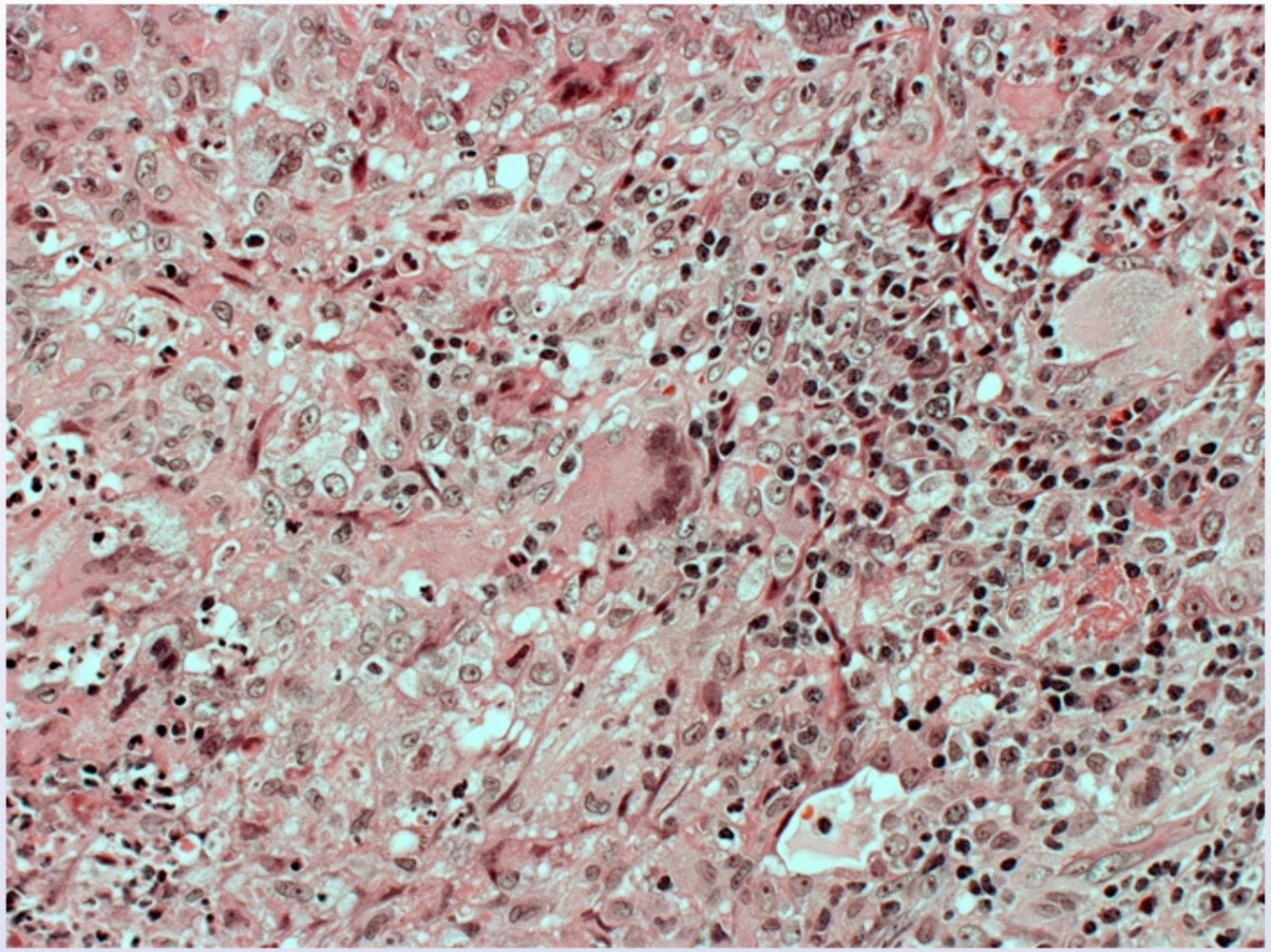

Which of the following substances is most important for driving the development of this patient's observed microscopic lesion?

A. C3a

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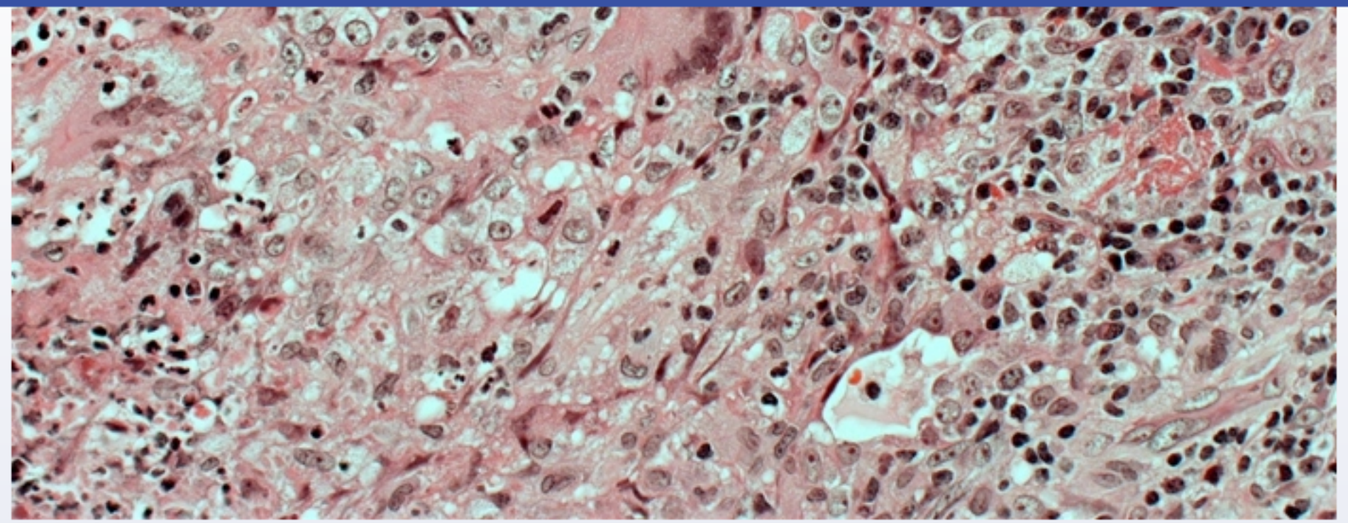

Which of the following substances is most important for driving the development of this patient's observed microscopic lesion?

A. C3a

B. Fibroblast growth factor

C. Granulocyte-macrophage colony-stimulating factor

D. IL-4

E. Interferon-alpha

F. Interferon-gamma

Submit

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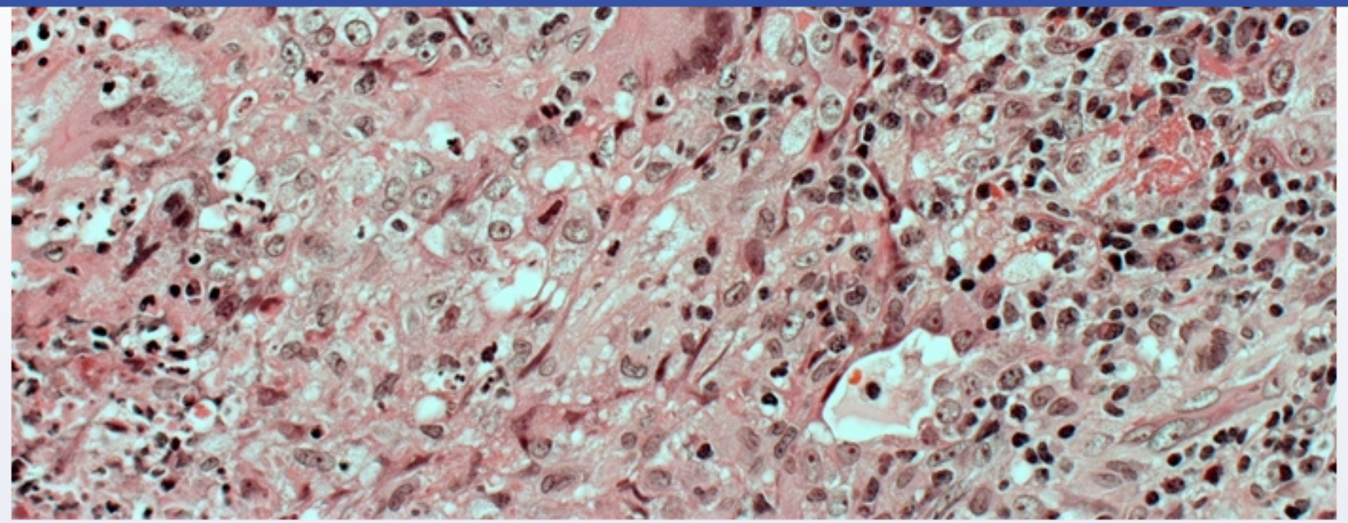

Which of the following substances is most important for driving the development of this patient's observed microscopic lesion?

A. C3a (2%)

B. Fibroblast growth factor (10%)

C. Granulocyte-macrophage colony-stimulating factor (8%)

D. IL-4 (3%)

E. Interferon-alpha (5%)

✓ F. Interferon-gamma (69%)

Omitted
Correct answer

69%
Answered correctly

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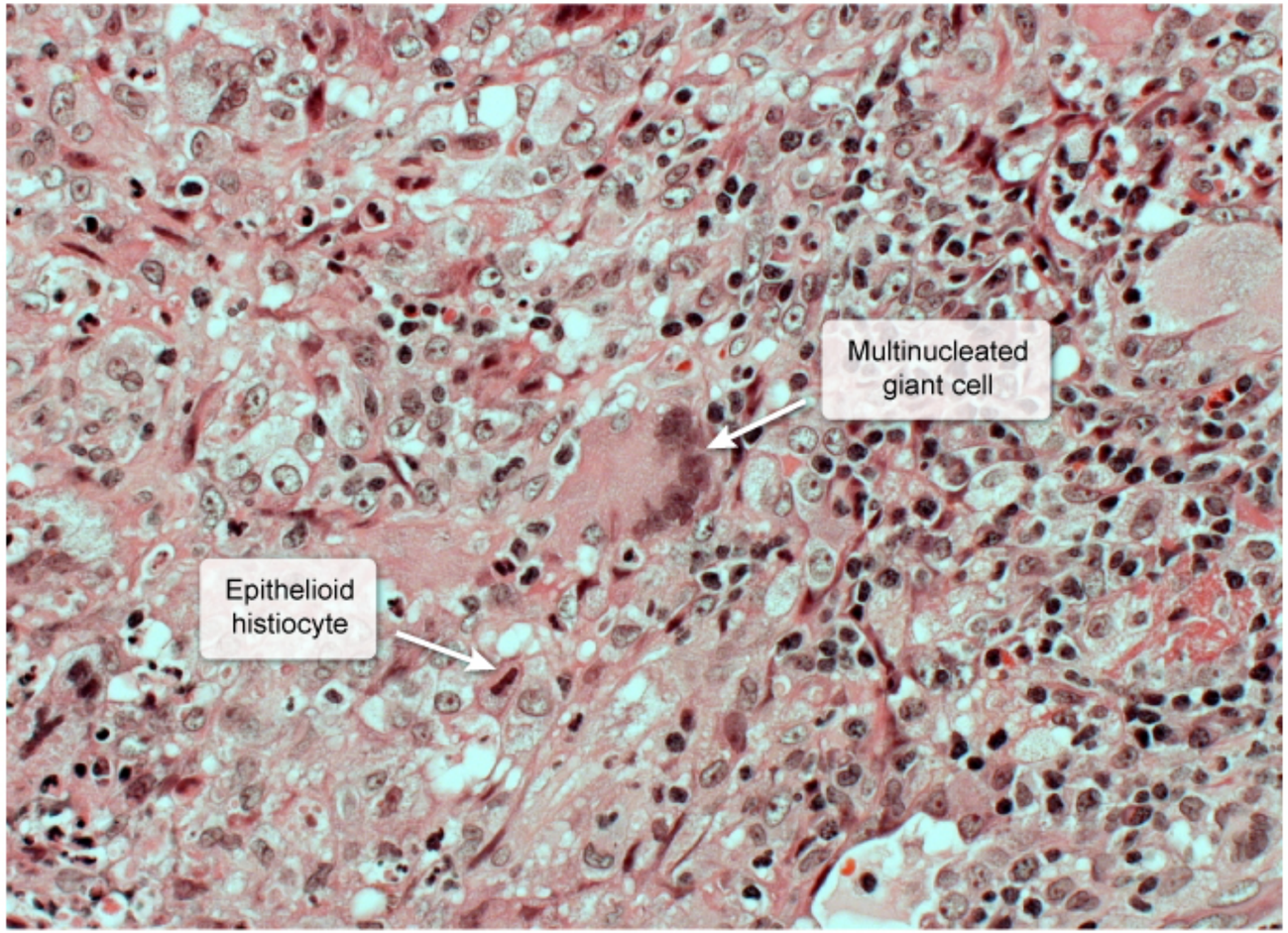
Granulomatous lung disease



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This patient has cough, fever, weight loss, and an upper lobe lesion on chest x-ray, raising strong suspicion for **active pulmonary tuberculosis**.

Mycobacterium tuberculosis cannot be visualized on Gram stain due to the high lipid content (mycolic acid) of its cell wall. Most cases are

This patient has cough, fever, weight loss, and an upper lobe lesion on chest x-ray, raising strong suspicion for **active pulmonary tuberculosis**. *Mycobacterium tuberculosis* cannot be visualized on Gram stain due to the high lipid content (mycolic acid) of its cell wall. Most cases are diagnosed by acid-fast sputum testing and culture, but tissue microscopy typically shows granulomas characterized by **epithelioid histiocytes** and **multinucleated Langhans giant cells**.

Granulomas often form after tissue macrophages encounter pathogens or substances that cannot be easily digested or removed. *M tuberculosis* can evade intracellular killing by macrophages and reproduce within phagolysosomes. Infected macrophages present mycobacterial antigens to naïve CD4 helper T cells in pulmonary lymph nodes and secrete IL-12, which induces activated T helper cells to differentiate into **T helper subtype 1 (Th1) cells**.

Proliferating Th1 cells migrate to sites of infection, where they release **interferon-gamma**, which **activates macrophages**, improves intracellular killing of ingested mycobacteria, and recruits additional macrophages by increasing production of **tumor necrosis factor-alpha**. Activated macrophages can also limit the spread of mycobacteria by differentiating into epithelioid and giant cells that surround residual foci of mycobacteria, trapping them inside the necrotic, cheese-like area of a caseating granuloma.

(Choice A) C3a is a split product anaphylatoxin derived from C3. It stimulates the release of histamine by mast cells, which increases vascular permeability and vasodilation.

(Choice B) Fibroblast growth factor has a variety of proliferative effects, including stimulation of angiogenesis and fibroblast proliferation during formation of granulation tissue. It does not have a primary role in the formation of granulomas.

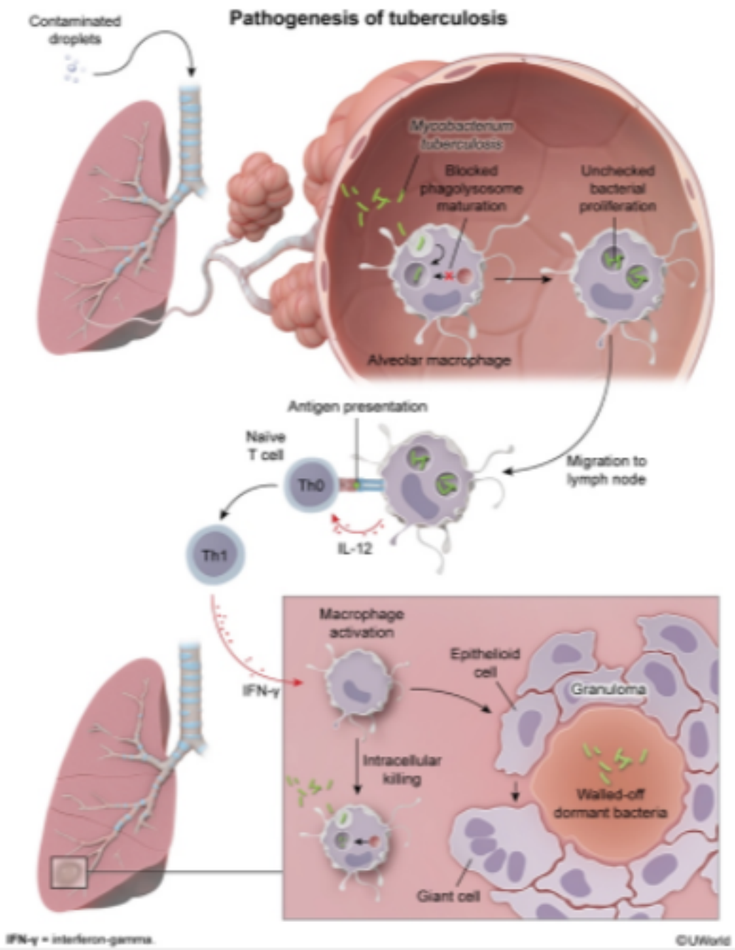
(Choice C) Granulocyte-macrophage colony-stimulating factor induces stem cell differentiation into monocytes and other granulocytes (eg, neutrophils, eosinophils). However, it does not induce granuloma formation.

(Choice D) IL-4 is a cytokine that stimulates the differentiation of naïve CD4 T cells into the Th2 subset, which plays an important role in humoral immunity and allergic reactions by stimulating B-cell proliferation and isotype switching to IgE.

(Choice E) Interferon-alpha is a primary mediator of the immune response to virus-infected cells. However, in contrast to interferon-gamma, it limits macrophage proliferation and does not drive granuloma formation.

Educational objective:

Exhibit Display



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Educational objective:

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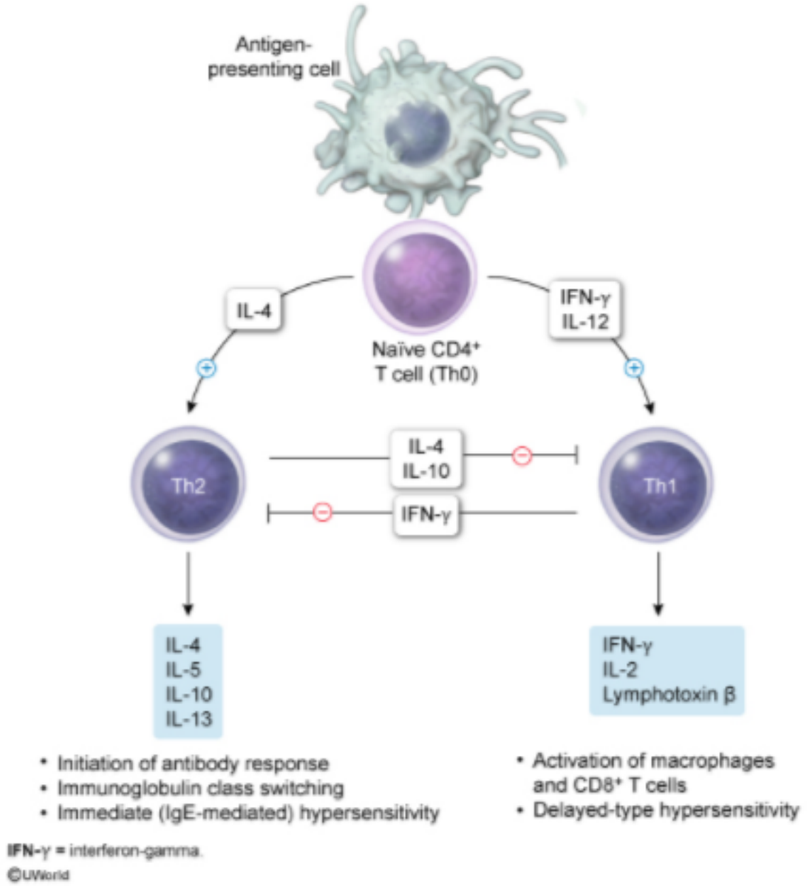
and **multinucleated Langhans giant cells**.

Exhibit Display

Factors in T helper cell differentiation



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epithelioid and Langhans giant cells to wall off extracellular mycobacteria within caseating granulomas.

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and **multinucleated Langhans giant cells**.

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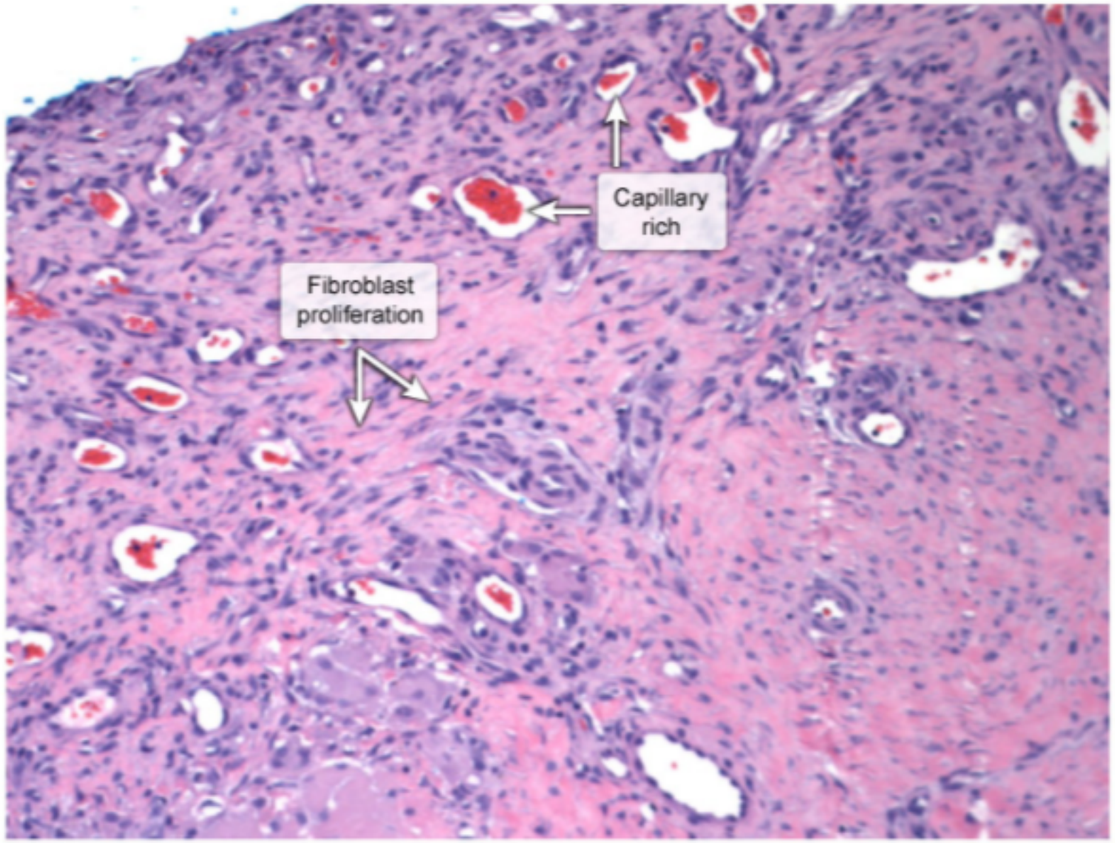

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macrophages can also limit the spread of mycobacteria by differentiating into epithelioid and giant cells that surround residual foci of mycobacteria, trapping them inside the necrotic, cheese-like area of a caseating granuloma.

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(Choice E) Interferon-alpha is a primary mediator of the immune response to virus-infected cells. However, in contrast to interferon-gamma, it limits macrophage proliferation and does not drive granuloma formation.

Educational objective:
T helper subtype 1 cells release interferon-gamma, leading to the activation of macrophages, a process critical for control of *Mycobacterium tuberculosis* infection. Activated macrophages form mature phagolysosomes that destroy phagocytosed mycobacteria and can differentiate into epithelioid and Langhans giant cells to wall off extracellular mycobacteria within caseating granulomas.

References

- Th1 and Th17 cells in tuberculosis: protection, pathology, and biomarkers.

Immunology	Pulmonary & Critical Care	Tuberculosis
Subject	System	Topic

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A 28-year-old man comes to the office with a 2-month history of dull low back pain and morning stiffness. The pain had an insidious onset, and the patient does not recall any recent trauma. He attempted treatment with acetaminophen and spinal manipulation, which did not provide relief. The patient has usually slept on his back but now must lie on his side to fall asleep easily. Past medical history is unremarkable. Vital signs are normal. Physical examination shows limited anterior flexion of the spine. There is no swelling or warmth of any peripheral joints. X-rays reveal narrowing of the sacroiliac joints. Which of the following is most strongly associated with this patient's disease?

- A. A specific human leukocyte antigen class I serotype
- B. A specific human leukocyte antigen class II serotype
- C. Auto-reactive immunoglobulin M antibodies
- D. Deficient complement component
- E. Selective immunoglobulin deficiency

Submit

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- ✓ A. A specific human leukocyte antigen class I serotype (61%)
- B. A specific human leukocyte antigen class II serotype (25%)
- C. Auto-reactive immunoglobulin M antibodies (11%)
- D. Deficient complement component (1%)
- E. Selective immunoglobulin deficiency (1%)

Omitted
Correct answer
A

61%
Answered correctly

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Explanation

Ankylosing spondylitis is a chronic inflammatory disorder of the sacroiliac joints and axial skeleton. It is most common in young and middle-aged men and presents with morning stiffness and low back pain. Ankylosing spondylitis is characterized by destruction of articular cartilage with resulting stiffness and fusion of axial joints. The **sacroiliac joints** are often tender to palpation, and the spine may have decreased range of motion. X-ray of the sacroiliac joints may reveal erosions, sclerosis, narrowing, and ultimately fusion of the joint spaces. Spine x-rays reveal sclerosis, ligamentous calcification, and vertebral fusion ("bamboo spine").

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Ankylosing spondylitis, reactive arthritis, arthritis associated with inflammatory bowel disease, and psoriatic arthritis are **seronegative spondyloarthropathies**, so-called due to the absence of serum rheumatoid factor. Patients with these diseases have a higher incidence of the **human leukocyte antigen (HLA) B27** allele compared to the general population, although most patients with HLA B27 will not develop spondyloarthropathies.

(Choice B) Class I HLA proteins (eg, HLA B27) are expressed by all nucleated cells and present endogenous antigens to $CD8^+$ cytotoxic T cells. By contrast, HLA class II proteins (eg, DR, DP, DQ alleles) are expressed by antigen-presenting cells (eg, macrophages, dendritic cells) and present predominantly foreign antigens to $CD4^+$ helper T cells. Conditions associated with HLA class II genotypes include rheumatoid arthritis, type I diabetes mellitus, and celiac disease.

(Choice C) Rheumatoid factor (immunoglobulin [Ig] M antibodies against self IgG) is present in the majority of patients with rheumatoid arthritis and may be seen in a variety of other autoimmune diseases as well as in some healthy individuals.

(Choice D) Complement component deficiencies are associated with recurrent infections and systemic lupus erythematosus.

(Choice E) IgA deficiency causes recurrent mucosal and respiratory infections and anaphylactic reactions after the transfusion of blood products.

Educational objective:
The seronegative spondyloarthropathies include ankylosing spondylitis, reactive arthritis, psoriatic arthritis, and arthritis associated with inflammatory bowel disease. Individuals expressing HLA B27 are at increased risk for the seronegative spondyloarthropathies.

References

- The genetics of ankylosing spondylitis and axial spondyloarthritis.

Immunology Rheumatology/Orthopedics & Sports Ankylosing spondylitis

A 25-year-old man comes to the office due to a 1-month history of increasing abdominal girth and swollen extremities. His BMI is 32 kg/m^2. Laboratory evaluation shows decreased serum albumin and hypercholesterolemia, and urinalysis reveals heavy proteinuria and fatty casts. A renal biopsy shows findings consistent with focal segmental glomerulosclerosis. Despite aggressive medical management, the patient requires a kidney transplant from his younger sister, who is a 5 out of 6 HLA antigen match. As a part of his posttransplant immunosuppressive regimen, he takes a medication that inhibits lymphocyte proliferation by directly blocking interleukin-2 signal transduction. This mechanism best describes which of the following drugs?

A. Bortezomib
B. Mycophenolate
C. Prednisone
D. Rituximab
E. Sirolimus

Submit

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A. Bortezomib (7%)
B. Mycophenolate (8%)
C. Prednisone (7%)
D. Rituximab (15%)
✓ E. Sirolimus (61%)

Omitted
Correct answer
E

61%
Answered correctly

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Explanation

Mechanism of action of common immunosuppressants

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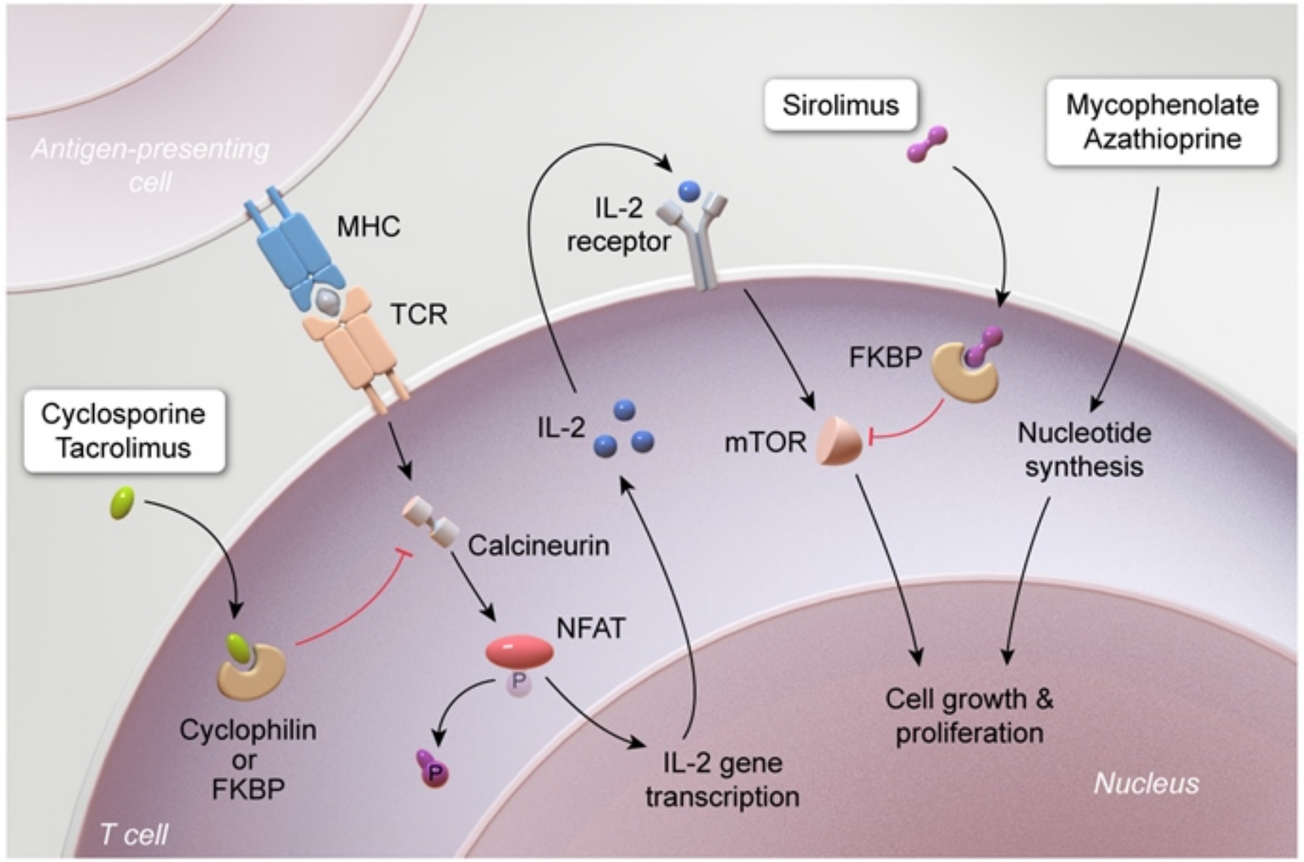

FKBP = FK506-binding protein; **MHC** = major histocompatibility complex; **mTOR** = mammalian target of rapamycin; **NFAT** = nuclear factor of activated T cells; **TCR** = T cell receptor.

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Unless a transplanted kidney is obtained from a genetically identical donor (eg, identical twin), chronic **immunosuppression therapy** is needed to help prevent organ rejection. **Sirolimus** is commonly used as part of the immunosuppression regimen for solid organ transplants. It functions as

Unless a transplanted kidney is obtained from a genetically identical donor (eg, identical twin), chronic **immunosuppression therapy** is needed to help prevent organ rejection. **Sirolimus** is commonly used as part of the immunosuppression regimen for solid organ transplants. It functions as a proliferation signal inhibitor by targeting the mTOR (mammalian target of rapamycin) signaling pathway, an important stimulator of cell growth and proliferation. Specifically, sirolimus binds to the immunophilin FK binding protein (FKBP), forming a complex that **inhibits mTOR**. This leads to **interruption of IL-2 signal transduction**, preventing G1 to S phase progression and lymphocyte proliferation.

Calcineurin inhibitors (eg, tacrolimus, cyclosporine) are other commonly used immunosuppression medications that function by blocking the translocation of nuclear factor of activated T-cells (NFAT), resulting in reduced transcription of IL-2.

(Choice A) Bortezomib binds and inhibits the 26S proteasome. In multiple myeloma, bortezomib can facilitate apoptosis of neoplastic cells by preventing degradation of proapoptotic factors.

(Choice B) Mycophenolate reversibly inhibits inosine monophosphate dehydrogenase. This blocks a critical step in the de novo synthesis of purine nucleotides that is required for proliferation of activated lymphocytes. Because most other cells have an alternative pathway for purine synthesis that lymphocytes lack, mycophenolate is relatively specific for suppression of B and T cells.

(Choice C) Prednisone and other glucocorticoids bind to cytoplasmic receptors, translocate to the nucleus, and then inhibit the transcription of genes that encode IL-2 and other inflammatory mediators.

(Choice D) Rituximab is a chimeric antibody directed against the CD20 antigen (specific to B lymphocytes). It depletes B cells (and reduces antibody production) through multiple pathways, including complement-mediated lysis, antibody-dependent cytotoxicity (via natural killer cells), and induction of lymphocyte apoptosis.

Educational objective:
Sirolimus binds to the immunophilin FK binding protein (FKBP) in the cytoplasm, forming a complex that binds and inhibits mTOR (mammalian target of rapamycin). Inhibition of mTOR signaling blocks IL-2 signal transduction and prevents cell cycle progression and lymphocyte proliferation.

Immunology	Renal, Urinary Systems & Electrolytes	Transplant rejection
Subject	System	Topic

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Immunology	Renal, Urinary Systems & Electrolytes	Transplant rejection
Subject	System	Topic

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A 4-year-old boy is being evaluated due to severe and recurrent infections. He has been hospitalized 3 times with pneumonia since birth. He has also had multiple skin infections that have required treatment with antibiotic and antifungal agents. The patient's neutrophils fail to turn blue following exposure to nitroblue tetrazolium. Which of the following substances is most likely produced by the microorganisms responsible for this patient's infections?

A. β-lactamase
B. Catalase
C. Coagulase
D. Lecithinase
E. Polysaccharide capsule

Submit

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- A. β-lactamase (2%)
- ✓ B. Catalase (84%)
- C. Coagulase (2%)
- D. Lecithinase (2%)
- E. Polysaccharide capsule (8%)

Omitted
Correct answer
B

84%
Answered correctly

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Explanation

The failure of this patient's neutrophils to turn blue on **nitroblue tetrazolium testing** is characteristic of chronic granulomatous disease, a condition most often caused by an X-linked mutation affecting **NADPH oxidase**. This enzyme normally functions within activated phagocytes to produce **reactive oxygen species** (eg, $O_2^{\cdot-}$, H_2O_2, $HO^{\cdot}$) that act directly as antimicrobial agents and also activate **granule proteases** (eg, elastase, cathepsin G) present in phagosomes. Inactivating mutations in NADPH oxidase cause **impaired intracellular killing** by neutrophils and macrophages, leading to **recurrent bacterial and fungal infections**. These infections are usually caused by **catalase-positive** organisms that can destroy the hydrogen peroxide produced by their own metabolic activity. In contrast, catalase-negative organisms cannot prevent

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(Choice A) β-lactamase is an enzyme produced by bacteria that confers resistance to β-lactam antibiotics (eg, penicillin). In an effort to overcome bacterial production of β-lactamase, penicillinase-resistant penicillins (eg, methicillin, oxacillin, nafcillin) and β-lactamase inhibitors (eg, clavulanic acid, tazobactam, sulbactam) were developed.

(Choice C) Coagulase is an enzyme produced by *Staphylococcus aureus* that activates prothrombin, resulting in the conversion of fibrinogen to fibrin. This process leads to fibrin-coating of the organism and resistance to phagocytosis.

(Choice D) Lecithinase (α toxin) is an enzyme with phospholipase C activity and the major virulence factor produced by *Clostridium perfringens*. The toxin increases platelet aggregation and adherence molecule expression on leukocytes and endothelial cells, resulting in vasoocclusion and ischemic necrosis of affected tissues.

(Choice E) The polysaccharide capsule expressed by some organisms (eg, *Haemophilus influenzae, Streptococcus pneumoniae*) inhibits phagocytosis by macrophages and neutrophils. Recognition of capsular antigens by the immune system leads to effective phagocytosis and killing of encapsulated organisms.

Educational objective:
Chronic granulomatous disease is an X-linked disorder resulting from deficiency of NADPH oxidase, the enzyme responsible for formation of reactive oxygen species in phagosomes. Neutrophils affected by this disorder are unable to kill catalase-producing organisms, resulting in recurrent bacterial and fungal infections that frequently involve the lungs, skin, and lymph nodes.

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Educational objective:
Chronic granulomatous di reactive oxygen species i recurrent bacterial and fu

Exhibit Display

Features of chronic granulomatous disease	
Pathogenesis	• Inactivating mutation affecting **NADPH oxidase** • Impaired respiratory burst inhibits phagocytic **intracellular killing**
Clinical manifestations	• Recurrent infections with **catalase-positive** bacteria & fungi • Lungs, skin, lymph nodes & liver most commonly involved • Diffuse **granuloma formation**
Diagnosis	Measurement of **neutrophil superoxide production**: • DHR flow cytometry (preferred) • NBT testing

DHR = dihydrorhodamine; **NBT** = nitroblue tetrazolium.

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Immunology	Infectious Diseases	Primary immunodeficiency disorder
Subject	System	Topic

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A 2-year-old boy is brought to the emergency department due to wheezing and difficulty breathing. The patient had been trick-or-treating with his parents and ate several packs of candy containing peanuts. After he receives an intramuscular epinephrine injection, his symptoms resolve. At a follow up appointment, an allergy specialist places droplets of various allergens on the patient's skin and punctures the epidermis at each site. After 15 minutes, the skin at the site with peanut extract is erythematous with a raised, itchy bump that improves by the time the family leaves the office. Four hours later, the parents notice a hard, red swelling at the puncture site. Which of the following is most likely involved in this secondary reaction?

A. Cell lysis following IgG autoantibody binding

B. Complement activation by immune complexes

C. Epithelial damage by major basic protein

D. IgE-mediated histamine release from mast cells

E. Interferon gamma release from $CD4^+$ T cells

Submit

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- A. Cell lysis following IgG autoantibody binding (3%)
- B. Complement activation by immune complexes (13%)
- ✓ C. Epithelial damage by major basic protein (31%)
- D. IgE-mediated histamine release from mast cells (17%)
- E. Interferon gamma release from $CD4^+$ T cells (33%)

Omitted
Correct answer
C

31%
Answered correctly

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Explanation

Cutaneous type 1 hypersensitivity reactions

Initial exposure Repeat exposure

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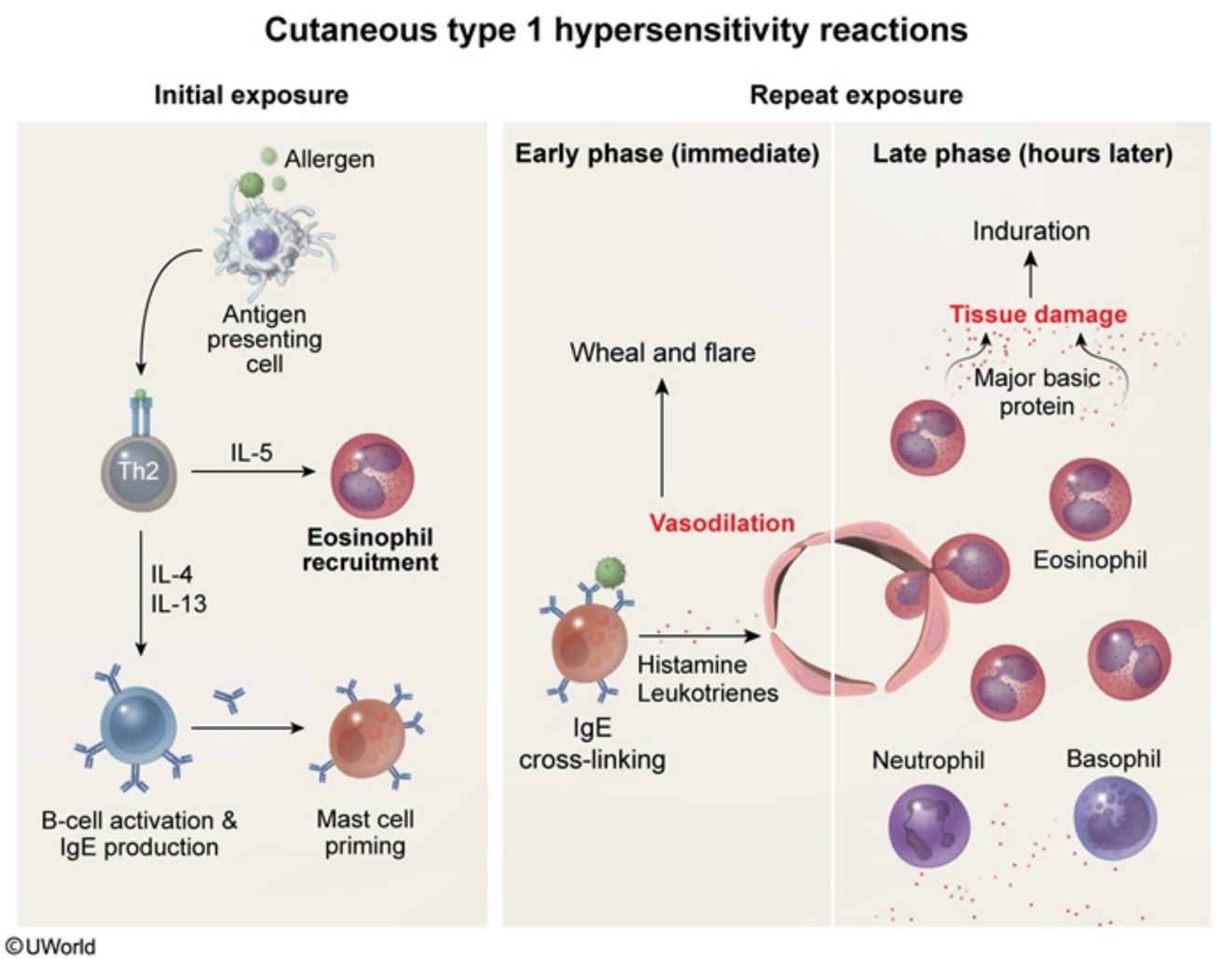

Following skin prick testing, this patient developed an erythematous, edematous welt that was followed 4 hours later by an indurated skin lesion. These findings are consistent with the early and late phases of a **type I hypersensitivity reaction**.

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After first exposure to an allergen (eg, peanuts), antigen specific IgE is produced by B-cells and binds to the surface of mast cells. If repeat exposure occurs, the bound IgE can cross-link and stimulate the release of preformed histamine and leukotrienes that cause vasodilation and increased capillary permeability. The result is a rapid (eg, minutes after exposure) **early-phase** type I hypersensitivity response characterized by superficial dermal edema and erythema (eg, wheal and flare reaction) that can progress to a more systemic response (eg, anaphylaxis) **(Choice D)**.

IgE also initiates the **late phase** of a type I hypersensitivity reaction by stimulating type 2 helper T cells to release cytokines (eg, IL-5) that activate **eosinophils**. Cationic proteins (eg, **major basic protein**, eosinophil peroxidase) released from eosinophils cause **tissue damage**, which usually manifests as a palpable, **indurated lesion** 2-10 hours following the early-phase reaction.

(Choice A) Binding of preformed IgG antibodies to cell surface antigens initiates cell lysis mediated by complement and/or natural killer cells (type II hypersensitivity reactions). These reactions can develop hours to days after exposure to an antigen (eg, medications, transfused red blood cells), resulting in destruction of erythrocytes (causing fatigue, pallor), platelets (petechial bleeding), or leukocytes (fever, sepsis).

(Choice B) Immune complex-mediated complement activation causes tissue damage days to weeks after initial antigen exposure in type III hypersensitivity reactions. Immune complexes tend to deposit in the basement membrane of small blood vessels in the skin, kidneys, or joints, resulting in vasculitis.

(Choice E) In delayed (type IV) hypersensitivity reactions, $CD4^+$ T cells release cytokines (eg, interferon gamma) that promote T cell- and macrophage-mediated tissue damage. Although these reactions can also present as an indurated skin lesion (eg, tuberculosis skin testing), type IV hypersensitivity reactions develop over days (rather than hours) because of the time needed for cellular amplification.

Educational objective:
The late phase of dermatologic type I hypersensitivity reactions manifests as an indurated skin lesion hours after exposure to the allergen due to local tissue damage caused by major basic protein released from eosinophils. In contrast, type IV hypersensitivity reactions develop over days because of the time needed to produce a cell-mediated immune response.

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Following skin prick testing, this patient developed an erythematous, edematous welt that was followed 4 hours later by an indurated skin lesion.

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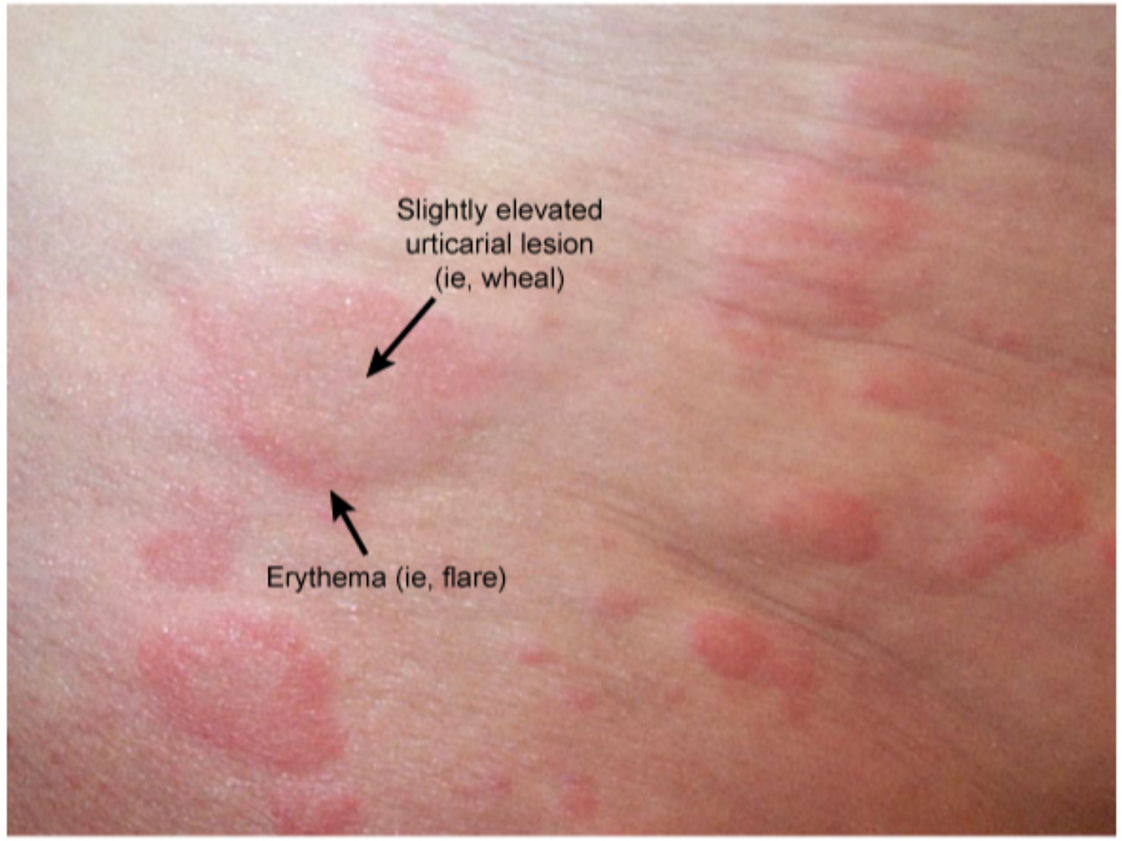
Wheal and flare



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increased capillary permeability. The result is a rapid (eg, minutes after exposure) **early-phase** type I hypersensitivity response characterized by superficial dermal edema and erythema (eg, wheal and flare reaction) that can progress to a more systemic response (eg, anaphylaxis) **(Choice D)**.

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(Choice E) In delayed (type IV) hypersensitivity reactions, $CD4^+$ T cells release cytokines (eg, interferon gamma) that promote T cell- and macrophage-mediated tissue damage. Although these reactions can also present as an indurated skin lesion (eg, tuberculosis skin testing), type IV hypersensitivity reactions develop over days (rather than hours) because of the time needed for cellular amplification.

Educational objective:
The late phase of dermatologic type I hypersensitivity reactions manifests as an indurated skin lesion hours after exposure to the allergen due to local tissue damage caused by major basic protein released from eosinophils. In contrast, type IV hypersensitivity reactions develop over days because of the time needed to produce a cell-mediated immune response.

Immunology	Dermatology	Hypersensitivity reactions
Subject	System	Topic

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increased capillary permeability. The result is a rapid (eg, minutes after exposure) **early-phase** type I hypersensitivity response characterized

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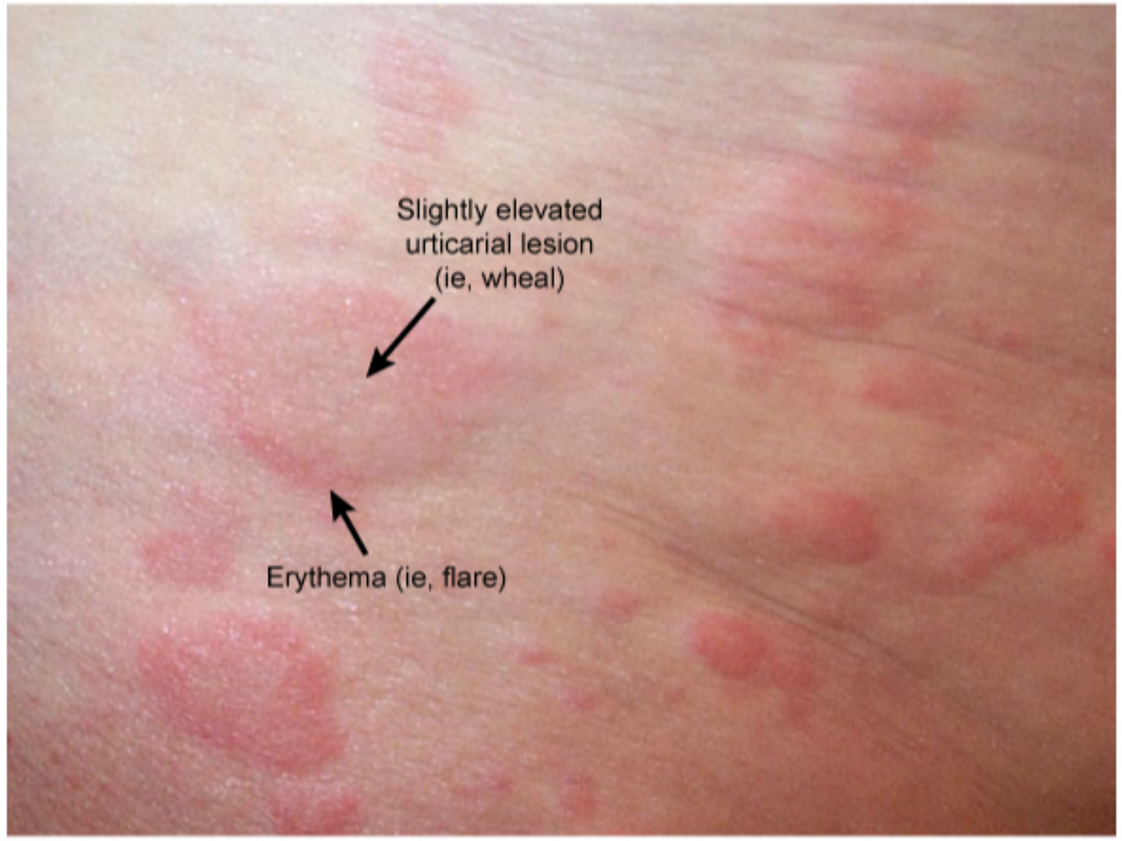
Wheal and flare



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A 24-year-old man burns his hand after grasping the handle of a hot pan while preparing a meal. Several minutes later, both the initial burn and the area around it are red without blistering. When he presses on the burn, the tissue blanches. Which of the following is most likely contributing to the reaction observed in this patient?

A. Gaps between endothelial cells in venules

B. Histamine release from mast cells

C. Neutrophil extravasation and degranulation

D. PDGF–mediated vascular proliferation

E. Prostaglandins produced by platelets

Submit

A 24-year-old man burns his hand after grasping the handle of a hot pan while preparing a meal. Several minutes later, both the initial burn and the area around it are red without blistering. When he presses on the burn, the tissue blanches. Which of the following is most likely contributing to the reaction observed in this patient?

- A. Gaps between endothelial cells in venules (35%)
- ✓ B. Histamine release from mast cells (26%)
- C. Neutrophil extravasation and degranulation (7%)
- D. PDGF–mediated vascular proliferation (6%)
- E. Prostaglandins produced by platelets (23%)

Omitted
Correct answer
B

26%
Answered correctly

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03/21/2020
Last Updated

Explanation

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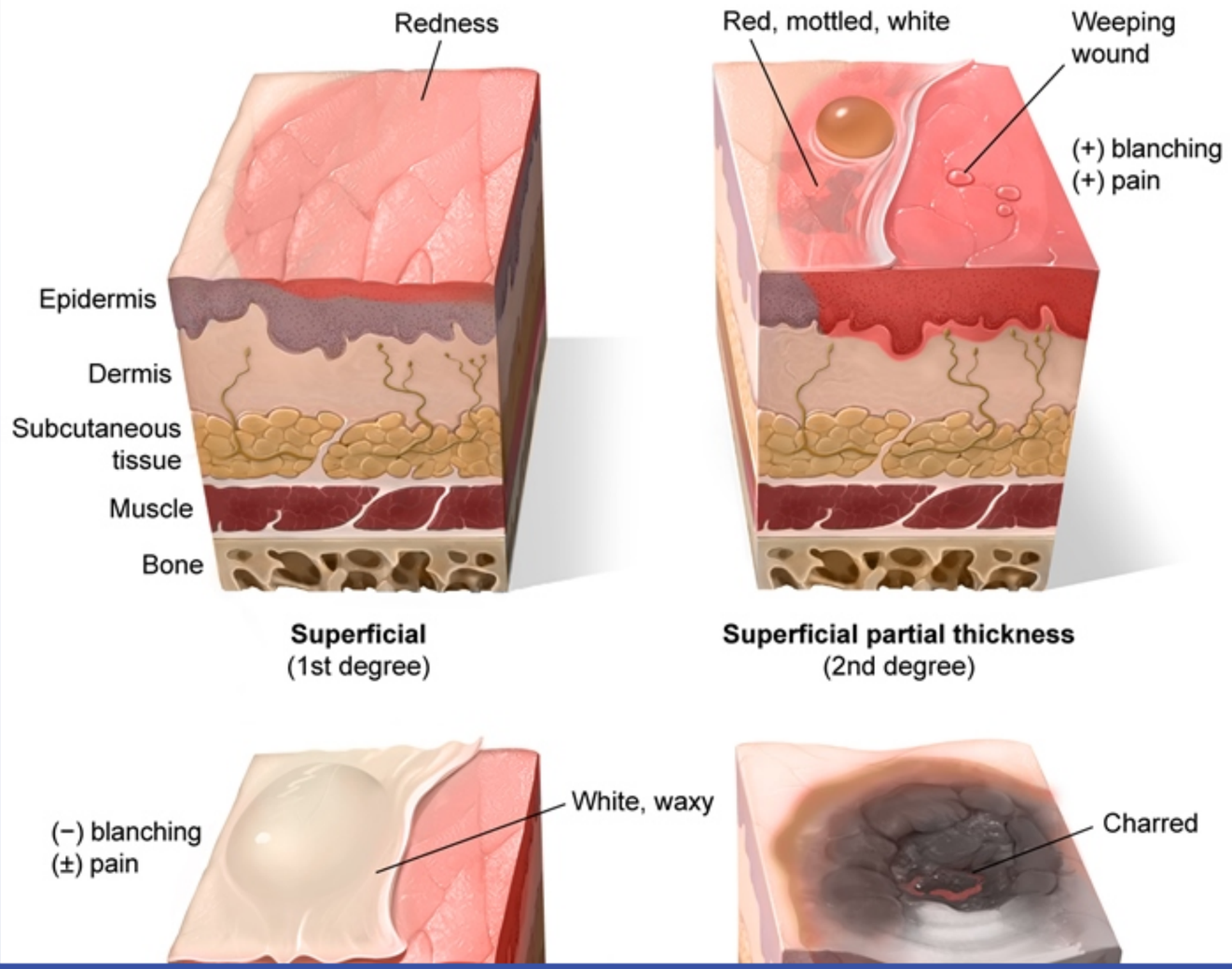
Burn classification



Superficial
(1st degree)

Superficial partial thickness
(2nd degree)

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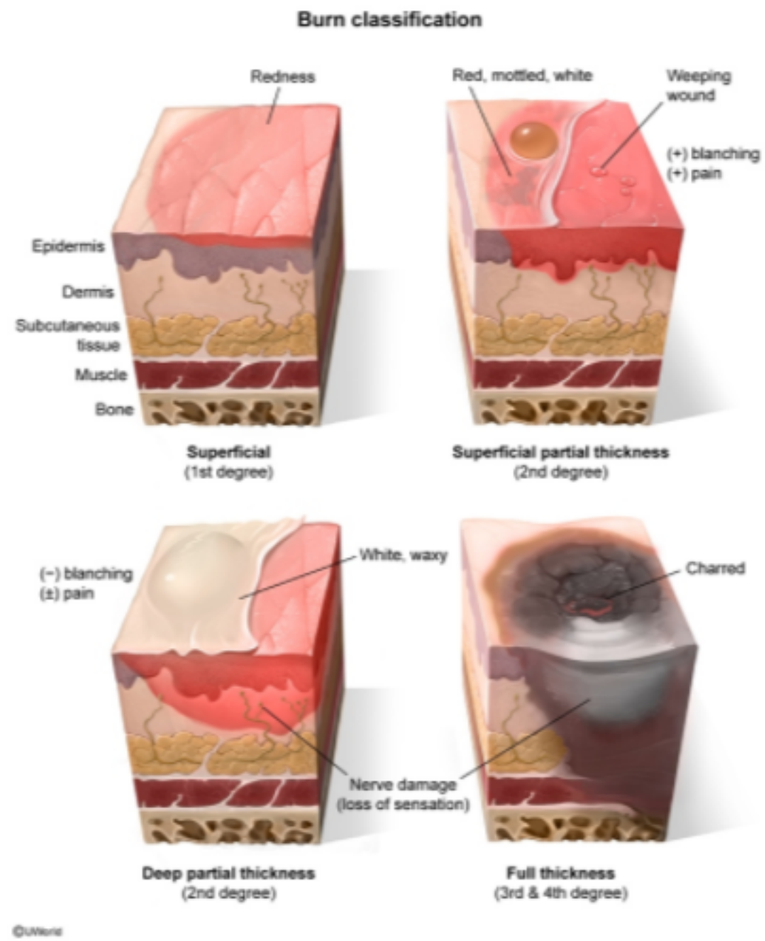

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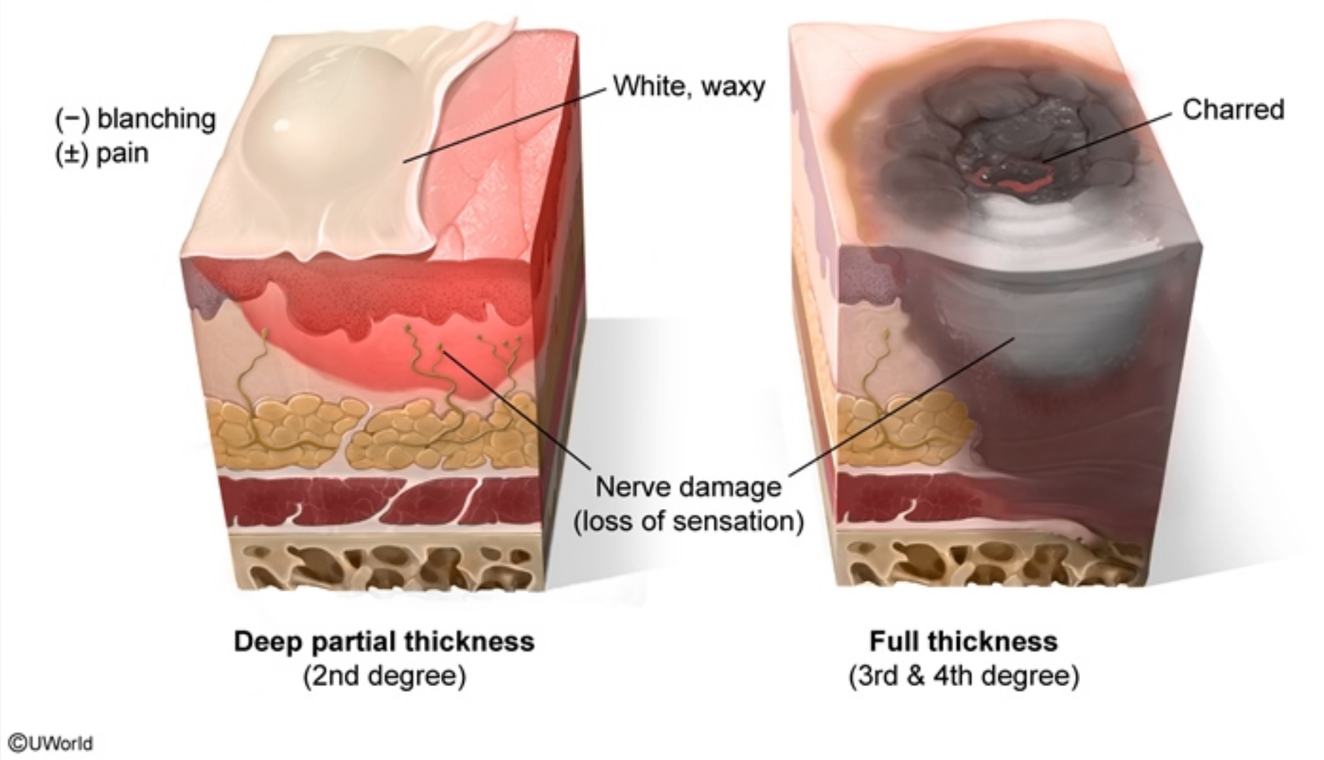

This patient has **erythema** that blanches without blistering, which is characteristic of a **superficial burn**. Burn wounds are classified according to depth based on which layers of cutaneous and subcutaneous tissues are damaged:

- Superficial burns damage only the epidermis.
- Superficial partial-thickness burns damage the epidermis and upper dermis.
- Deep partial-thickness burns damage the epidermis and most of the dermis.
- Full-thickness burns damage the entire dermis and may extend into the fat, muscle, and/or bone.

The morphologic changes in burns occur due to both direct tissue damage and **inflammatory mediators** released from epidermal and immune cells. Release of **histamine** and other preformed vasoactive mediators from **mast cells** in the minutes following a burn leads to dilation of

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The morphologic changes in burns occur due to both direct tissue damage and **inflammatory mediators** released from epidermal and immune cells. Release of **histamine** and other preformed vasoactive mediators from **mast cells** in the minutes following a burn leads to dilation of superficial skin capillaries. This results in blanching erythema (ie, temporary whitening with pressure due to capillary collapse) that extends to the area surrounding the initial burn.

Deeper (eg, partial-thickness) burns affect dermal structures such as nerve endings and venules in addition to the epidermis. Nerve damage can lead to loss of sensation while damage to venules can result in fluid extravasation through gaps between injured venule endothelial cells. The result is a blister formed from a collection of serous fluid between the dermis and epidermis **(Choice A)**.

(Choices C and E) Platelets and neutrophils play an important role in healing after a thermal burn by releasing prostaglandins, cytokines, and growth factors that stimulate increased blood flow, inflammation, and tissue regrowth. Although both cells contribute to the erythema in and around a burn wound, these changes occur hours to days after the burn rather than minutes after, as in this patient.

(Choice D) Platelet-derived growth factor (PDGF) is released by platelets, macrophages, and endothelial cells and plays an important role in generating the vascular and fibroblast proliferation needed for normal wound healing over the days to weeks following the initial injury.

Educational objective:
The earliest morphologic change that occurs after a superficial thermal burn is erythema due to the release of preformed mediators (eg, histamine) from mast cells. Deeper (eg, partial-thickness) burn wounds form blisters due to fluid extravasation through gaps between damaged venule endothelial cells.

- Superficial partial-thickness burns damage the epidermis and upper dermis.
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Immunology	Dermatology	Thermal burn
Subject	System	Topic

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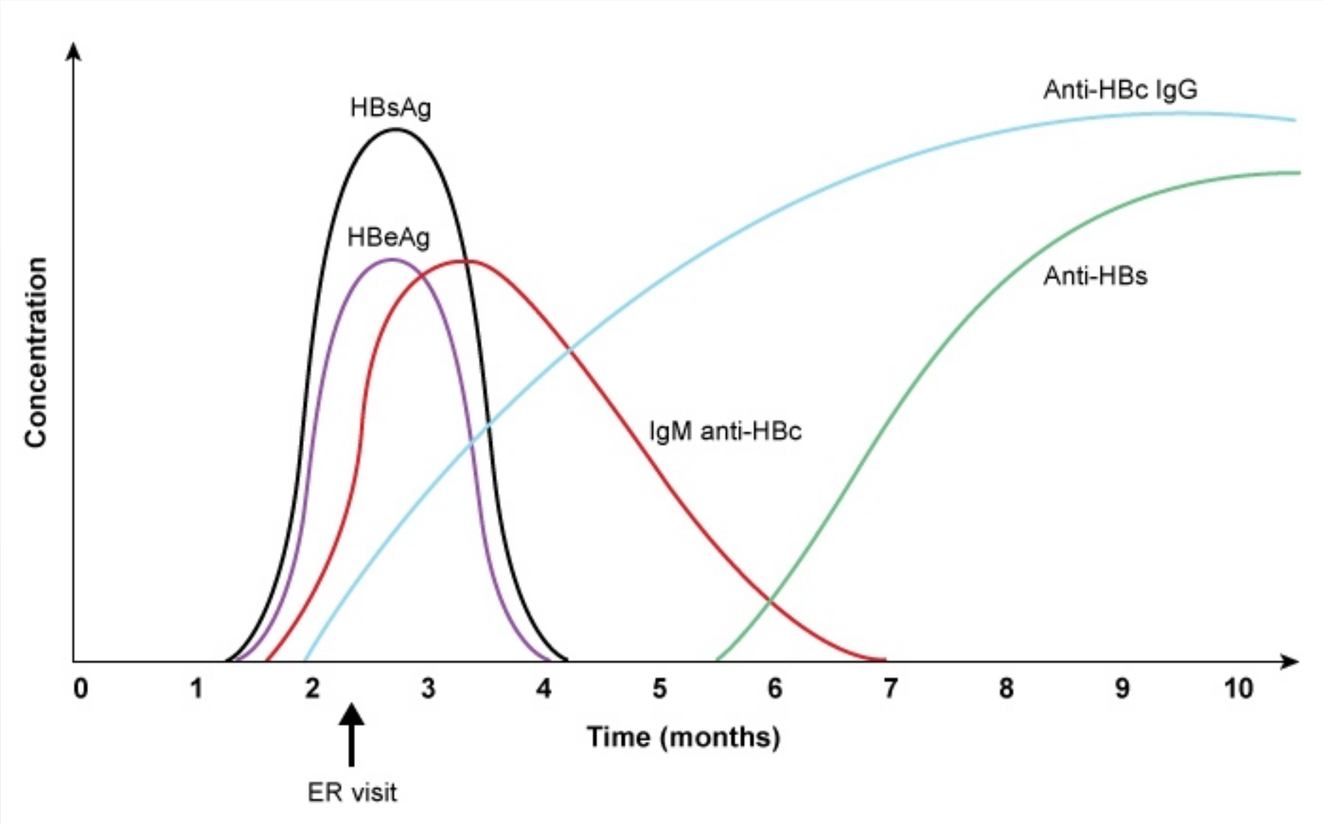
A 23-year-old man comes to the emergency department due to 7 days of fever and malaise. He has also had nausea and a poor appetite. The patient has no significant medical history but regularly uses injection drugs and has had multiple sexual partners. Temperature is 38 C (100.4 F). On physical examination, there is scleral icterus. A tender, smooth liver edge is palpable 4 cm below the right costal margin. Appropriate therapy is initiated. The following graph illustrates this patient's hepatitis B serologic markers over time.



Which of the following best explains these observed findings?

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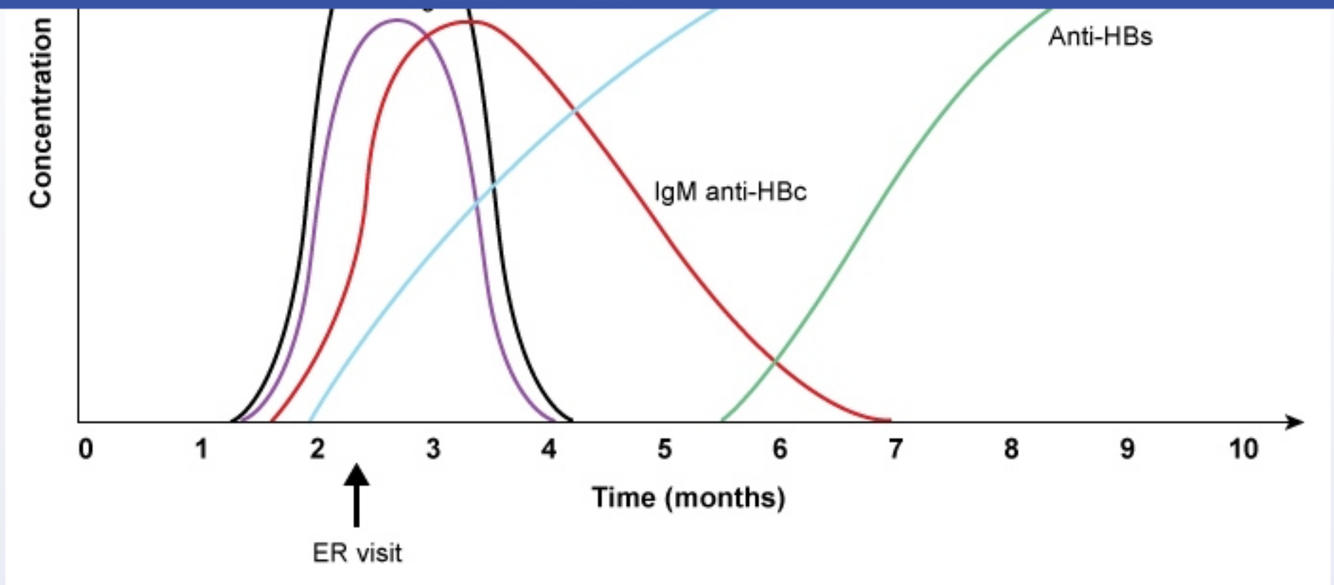

Which of the following best explains these observed findings?

- A. Acute hepatitis B that progressed to chronic hepatitis with high infectivity
- B. Acute hepatitis B that progressed to chronic hepatitis with low infectivity
- C. Acute exacerbation of pre-existing chronic hepatitis B infection
- D. Immunity against hepatitis B acquired from vaccination during the hospitalization
- E. Recovery from acute hepatitis B infection with immunity against reinfection

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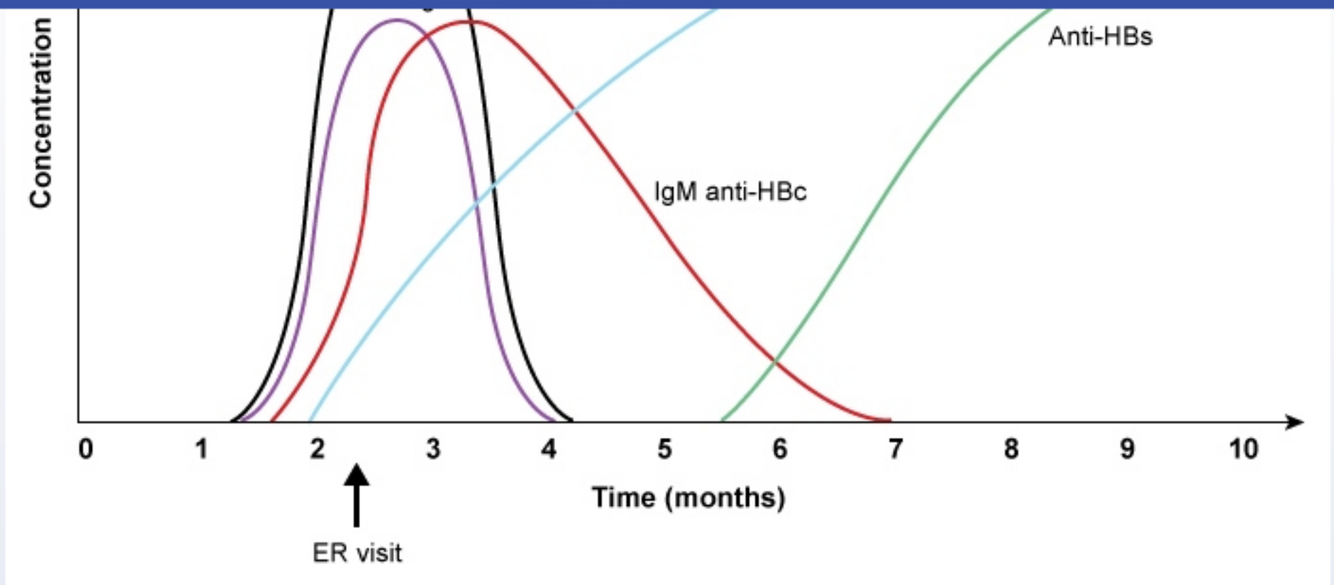

Which of the following best explains these observed findings?

A. Acute hepatitis B that progressed to chronic hepatitis with high infectivity (13%)

B. Acute hepatitis B that progressed to chronic hepatitis with low infectivity (12%)

C. Acute exacerbation of pre-existing chronic hepatitis B infection (3%)

D. Immunity against hepatitis B acquired from vaccination during the hospitalization (3%)

✓ E. Recovery from acute hepatitis B infection with immunity against reinfection (66%)

Omitted
Correct answer

66%
Answered correctly

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Importance of hepatitis B serological markers	
HBsAg	• HBV surface glycoproteins • Detectable during acute infection • Persistence >6 months = **chronic infection**
HBeAg	• HBV polypeptide • Detectable during acute infection • Indicates ↑ **viral replication** & infectivity
Anti-HBc IgM	• First sign of **acute** infection • Present during **window phase** prior to HBsAg & HBeAg
Anti-HBs	• Seen with cleared infection or vaccination • Confers long-term **immunity**
Anti-HBe	• Develops in cleared infection & later in chronic infection • Indicates ↓ **viral replication** & infectivity
Anti-HBc IgG	• Present in both acute & chronic infection • **Not present** after vaccination

Serologic evidence of **hepatitis B virus** (HBV) exposure is present in ~2 billion people worldwide. Perinatal transmission is most common in high-incidence areas (eg, sub-Saharan Africa). In low-prevalence countries such as the United States, Western Europe, and Canada, most cases arise due to unsafe sexual practices or **injection drug use**.

Serological markers for HBV can be used to distinguish between acute infection, chronic infection, and a protective vaccination response. **Acute** HBV infection is marked by the proliferation of the virus in hepatocytes with the release of viral antigens (**HBsAg**, **HBeAg**) and **HBV DNA** into the bloodstream and the generation of **IgM against HB core antigen**. Many patients with acute infection will have subclinical, anicteric disease, but approximately 30% develop several weeks or months of jaundice, fatigue, hepatomegaly, and elevated transaminases.

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Most adults with HBV clear the virus and generate protective immunity against future infection. This is reflected serologically by the following progression:

1. **Anti-HBe** antibodies develop 3-6 months after initial infection and are associated with the elimination of HBeAg. This correlates with reduced viral replication and infectivity.
2. HBsAg is eliminated around the time that HBeAg becomes undetectable.
3. **Anti-HBsAg** antibodies form several weeks/months later and provide **protective immunity** against future infection.

(Choices A and B) Patients with chronic hepatitis B have elevated HBsAg >6 months after initial infection. Chronic hepatitis B with high infectivity is represented by persistent elevation of HBsAg, HBeAg, and HBV DNA with no anti-HBe. Transition from high infectivity to low infectivity usually occurs years later and is marked by anti-HBe, the elimination of HBeAg, and the continued production of HBsAg.

(Choice C) Patients with an exacerbation of chronic hepatitis B have an abrupt increase in liver enzymes and increased levels of HBV DNA. Exacerbations are often asymptomatic, but some individuals develop symptoms of acute hepatitis.

(Choice D) Vaccination against hepatitis B would be identified by the presence of anti-HBs with no anti-HBc, anti-HBe, or viral antigens.

Educational objective:
The presence of anti-HBc and anti-HBs antibodies in the serum without detectable viral antigens indicates recovery from acute hepatitis B infection. In contrast, patients vaccinated against hepatitis B will have anti-HBs antibodies without detectable levels of anti-HBc. Chronic hepatitis B is indicated by persistent levels of HBsAg and HBV DNA in the serum.

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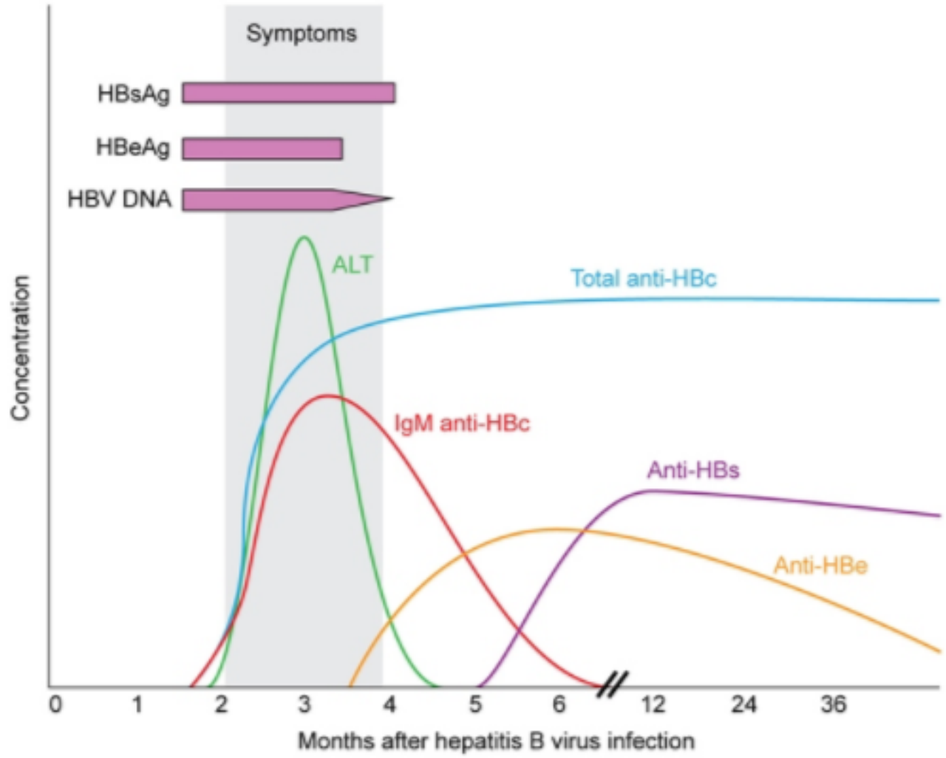
References

- The laboratory diagnosis of hepatitis B virus.

Serological markers for HBV can be used to distinguish between acute infection, chronic infection, and a protective vaccination response. **Acute**

Exhibit Display

Acute hepatitis B infection



ALT = alanine aminotransferase; **anti-HBc** = hepatitis B core antibody; **anti-HBe** = hepatitis B e antibody; **anti-HBs** = hepatitis B surface antibody; **HBeAg** = hepatitis B e antigen; **HBsAg** = hepatitis B surface antigen; **HBV** = hepatitis B virus.

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bloodstream and the generation of **IgM against HB core antigen**. Many patients with acute infection will have subclinical, anicteric disease, but

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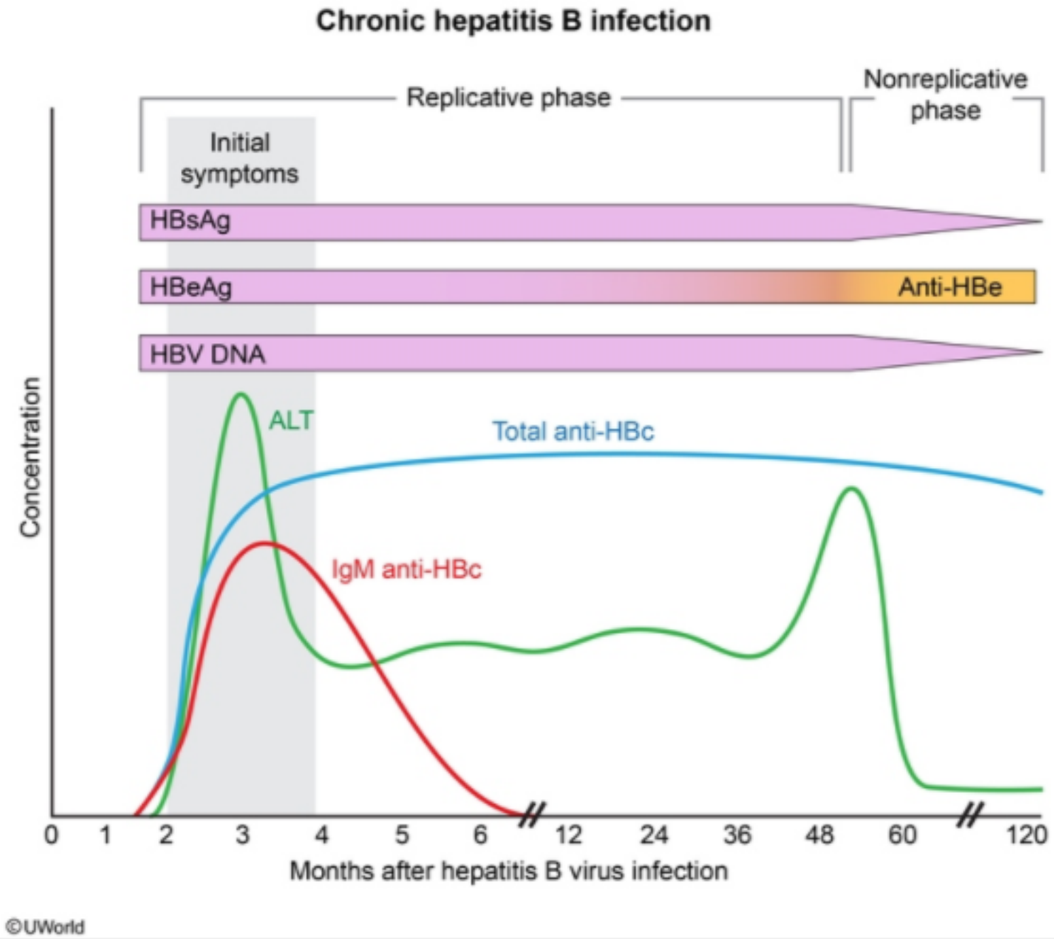

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A 19-year-old woman is brought to the emergency department after a motor vehicle collision. The patient's medical history includes celiac disease and 3 episodes of pneumonia. Her blood pressure is 80/45 mm Hg and pulse is 130/min. Physical examination reveals pallor, and ultrasound shows a splenic laceration. She receives a blood transfusion with O-negative packed red blood cells. During transfusion, the patient develops facial swelling, generalized hives, and shortness of breath. Which of the following is the most likely diagnosis in this patient?

A. ABO incompatibility

B. C1 inhibitor deficiency

C. Leukocyte adhesion deficiency

D. Selective IgA deficiency

E. Severe combined immune deficiency

Submit

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- A. ABO incompatibility (18%)
- B. C1 inhibitor deficiency (18%)
- C. Leukocyte adhesion deficiency (2%)
- ✓ D. Selective IgA deficiency (59%)
- E. Severe combined immune deficiency (2%)

Omitted
Correct answer
D

59%
Answered correctly

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Last Updated

Explanation

Selective IgA deficiency	
Clinical	• Usually asymptomatic • Recurrent sinopulmonary,

Selective IgA deficiency	
Clinical features	• Usually asymptomatic • Recurrent sinopulmonary, gastrointestinal infections • Autoimmune disease • Anaphylaxis during transfusions
Diagnosis	• Low or absent serum IgA levels • Normal IgG & IgM levels

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This patient has a history of recurrent pneumonia, a diagnosis of celiac disease, and an anaphylactic reaction during blood transfusion. These findings are highly suggestive of **selective IgA deficiency**, the most common primary immunodeficiency. Although most patients with IgA deficiency are asymptomatic, some may have recurrent **sinopulmonary** (eg, sinusitis, pneumonia) and **gastrointestinal** infections (eg, *Giardia*) due to absence of secretory IgA. Concomitant **autoimmune** disorders (eg, celiac disease) are also common.

Patients with severe IgA deficiency can form IgE antibodies directed against IgA (anti-IgA antibodies). Serum IgA levels are low or undetectable due to failure of B cells to differentiate into IgA-secreting plasma cells; serum IgG and IgM levels are normal. When transfused with **blood products** (eg, red blood cells, platelets, fresh frozen plasma) containing small amounts of IgA, these patients can develop potentially fatal **anaphylaxis**. Therefore, patients with severe IgA deficiency should wear medical alert bracelets and receive blood products that are washed of residual plasma or from an IgA-deficient donor.

(Choice A) Acute hemolytic reactions occur when a patient's preexisting IgM or IgG antibody cross-reacts with antigens (eg, A, B, Rh, Kell) in transfused blood. Reactions range from fever and chills to severe hemolysis and circulatory collapse. However, anaphylaxis is IgE-mediated and does not result from ABO incompatibility.

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(Choice B) C1 inhibitor deficiency causes hereditary angioedema that can be triggered by transfusions. Affected patients have angioedema but do not have urticaria or wheezing, both of which are present in this patient.

(Choice C) Leukocyte adhesion deficiency results in poor leukocyte adherence and transmigration through the vasculature. Affected patients present with recurrent skin and mucosal infections but are not at an increased risk for anaphylaxis during transfusion.

(Choice E) Severe combined immune deficiency results from failure of T cell development and leads to a severe defect of cell-mediated and humoral immunity. This disease causes severe bacterial, viral, and fungal infections beginning in infancy.

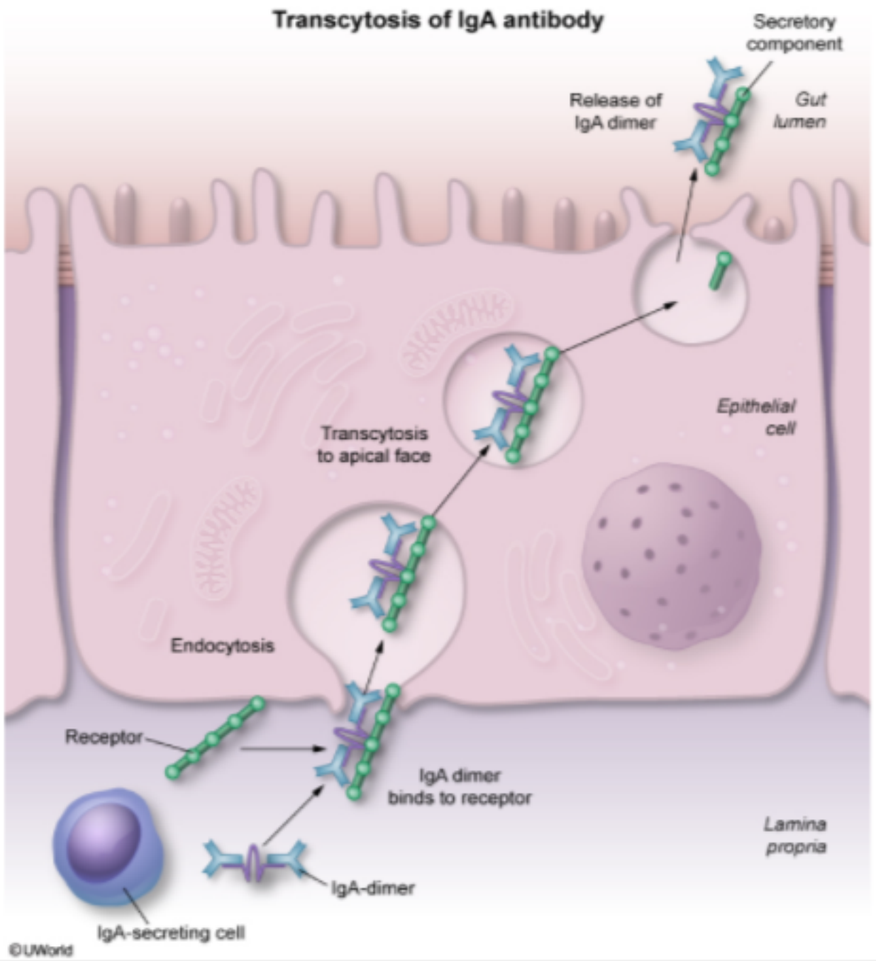
Educational objective:
Selective IgA deficiency is the most common primary immune deficiency and can present with recurrent sinopulmonary and gastrointestinal infections as well as autoimmune disease. Patients with severe IgA deficiency can have anaphylaxis during transfusion of blood products that contain small amounts of IgA.

References

- Selective IgA deficiency.

This patient has a history of recurrent pneumonia, a diagnosis of celiac disease, and an anaphylactic reaction during blood transfusion. These

Exhibit Display



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- Selective IgA deficiency.

due to failure of B cells to differentiate into IgA-secreting plasma cells; serum IgG and IgM levels are normal. When transfused with **blood products** (eg, red blood cells, platelets, fresh frozen plasma) containing small amounts of IgA, these patients can develop potentially fatal **anaphylaxis**. Therefore, patients with severe IgA deficiency should wear medical alert bracelets and receive blood products that are washed of residual plasma or from an IgA-deficient donor.

(Choice A) Acute hemolytic reactions occur when a patient's preexisting IgM or IgG antibody cross-reacts with antigens (eg, A, B, Rh, Kell) in transfused blood. Reactions range from fever and chills to severe hemolysis and circulatory collapse. However, anaphylaxis is IgE-mediated and does not result from ABO incompatibility.

(Choice B) C1 inhibitor deficiency causes hereditary angioedema that can be triggered by transfusions. Affected patients have angioedema but do not have urticaria or wheezing, both of which are present in this patient.

(Choice C) Leukocyte adhesion deficiency results in poor leukocyte adherence and transmigration through the vasculature. Affected patients present with recurrent skin and mucosal infections but are not at an increased risk for anaphylaxis during transfusion.

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References

- Selective IgA deficiency.

Immunology	Pulmonary & Critical Care	Selective iga deficiency
Subject	System	Topic

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A 55-year-old man is evaluated due to a nonhealing left forearm wound. The patient had an excisional biopsy of a suspicious skin lesion at the site of the wound several weeks ago. He has a history of uncontrolled type 2 diabetes mellitus and hypertension. Vital signs are within normal limits. Physical examination shows a 2.5-cm wound surrounded by erythema on the left forearm. Upregulation of which of the following would most likely improve fibroblast proliferation and reepithelization in this nonhealing wound?

A. Bradykinin release from endothelial cells

B. Cortisol release from the adrenal cortex

C. Glycation cross-links in collagen fibers

D. Production of IL-10 by macrophages

E. Release of reactive oxygen species from neutrophils

Submit

A 55-year-old man is evaluated due to a nonhealing left forearm wound. The patient had an excisional biopsy of a suspicious skin lesion at the site of the wound several weeks ago. He has a history of uncontrolled type 2 diabetes mellitus and hypertension. Vital signs are within normal limits. Physical examination shows a 2.5-cm wound surrounded by erythema on the left forearm. Upregulation of which of the following would most likely improve fibroblast proliferation and reepithelization in this nonhealing wound?

- A. Bradykinin release from endothelial cells (8%)
- B. Cortisol release from the adrenal cortex (2%)
- C. Glycation cross-links in collagen fibers (28%)
- ✓ D. Production of IL-10 by macrophages (58%)
- E. Release of reactive oxygen species from neutrophils (1%)

Omitted
Correct answer
D

58%
Answered correctly

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Time Spent

03/18/2020
Last Updated

Explanation

This patient with a history of uncontrolled diabetes mellitus has a nonhealing wound with evidence of ongoing inflammation (eg, erythema).

Wound healing normally progress through the inflammatory, proliferative, and remodeling phases. In the days after the initial injury, neutrophils and other immune cells are recruited to the wound and produce an **inflammatory response** that helps prevent bacterial overgrowth in the nutrient-rich environment of a healing wound. However, this inflammation also **impairs formation of granulation tissue** that is needed for normal wound healing. As healing progresses, release of growth factors and **anti-inflammatory cytokines** (eg, IL-10) by macrophages and

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In patients with diabetes mellitus, constitutively **elevated blood glucose** increases inflammation by stimulating the release of **proinflammatory cytokines** and reactive oxygen species from neutrophils **(Choice E)**. Elevated glucose also leads to a marked **decrease in IL-10** production that contributes to the increased susceptibility for chronic, **nonhealing wounds** and ulcers in patients with uncontrolled diabetes.

(Choice A) Bradykinin is a vasoactive inflammatory mediator that is normally produced by endothelial cells, macrophages, and platelets during the inflammatory phase of wound healing. Further upregulation of inflammatory mediators in patients with diabetes would most likely have a negative effect on fibroblast proliferation and reepithelialization.

(Choice B) Although a baseline level of cortisol production is required for normal wound healing, excess cortisol can impair both the inflammatory and proliferative components of wound healing. Patients with diabetes tend to have elevated cortisol levels; therefore, further cortisol elevation would not improve wound healing.

(Choice C) Excess glucose inhibits fibroblast migration and results in the nonenzymatic glycation of collagen fibers, which can prevent collagen cross-linking and can impair the structural integrity of a healing wound.

Educational objective:
Elevated blood glucose induces the release of reactive oxygen species and proinflammatory cytokines from neutrophils while inhibiting the production of anti-inflammatory cytokines (eg, IL-10) and growth factors needed for fibroblast proliferation and reepithelialization in a healing wound. As a result, patients with uncontrolled diabetes frequently have nonhealing wounds with evidence of ongoing inflammation.

Immunology	Dermatology	Wound healing
Subject	System	Topic

and other immune cells are recruited to the wound and produce an **inflammatory response** that helps prevent bacterial overgrowth in the nutrient-rich environment of a healing wound. However, this inflammation also **impairs formation of granulation tissue** that is needed for normal wound healing. As healing progresses, release of growth factors and **anti-inflammatory cytokines** (eg, IL-10) by macrophages and regulatory T cells suppresses the inflammatory response, **facilitating fibroblast proliferation** and reepithelialization of the wound.

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Immunology	Dermatology	Wound healing
Subject	System	Topic

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A 57-year-old man underwent lung transplantation for severe emphysema 2 years ago. Over the last 6 months, he has had increasing exertional dyspnea and dry cough. The patient has adhered to his medical regimen. He does not smoke and has no exposure to secondhand smoke. Physical examination shows scattered bilateral rales and end-expiratory squeaks. Cardiac auscultation reveals no murmurs or additional sounds. Spirometry demonstrates markedly decreased FEV1 compared with findings 6 months prior, although the FVC remains largely unchanged. Chronic lung transplant rejection is suspected, and bronchoscopy with transbronchial biopsy is planned. Histopathology is most likely to show injury predominantly involving which of the following structures?

A. Alveolar walls
B. Large airways
C. Pleural membranes
D. Small airways
E. Small blood vessels

Submit

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- A. Alveolar walls (32%)
- B. Large airways (6%)
- C. Pleural membranes (2%)
- ✓ D. Small airways (38%)
- E. Small blood vessels (20%)

Omitted
Correct answer
D

38%
Answered correctly

02 secs
Time Spent

05/14/2020
Last Updated

Explanation

Lung transplant rejection			
Type	Onset	Etiology	Pathophysiology

Lung transplant rejection			
Type	**Onset**	**Etiology**	**Pathophysiology**
Hyperacute	Minutes to hours	**Preformed host antibodies** to donor ABO or HLA	Neutrophilic infiltration with fibrinoid necrosis and thrombosis
Acute	≤6 months	Cell-mediated response to mismatched donor HLA	Perivascular (small lung vessels) & submucosal (bronchiole) lymphocytic infiltrates
Chronic	Months or years	Chronic, low-grade, cell-mediated response to HLA antigens	Submucosal inflammation → granulation, scarring & **bronchiolitis obliterans**

HLA = human leukocyte antigen.

Although patients who undergo organ transplantation receive immunosuppressive therapy, rejection reactions still commonly occur. The severity and timing of the rejection depends on the degree of difference between the donor and recipient major histocompatibility complex antigens in addition to other variables.

Chronic lung transplant rejection is marked by submucosal lymphocytic inflammation in the walls of the **small airways**. Subsequent ingrowth of granulation tissue into the lumen leads to airway obstruction and obliteration (**bronchiolitis obliterans**). Patients usually present with **slowly worsening dyspnea** and dry cough that begins **months or years after transplantation**. Lung examination may reveal end-expiratory squeaks or pops, and spirometry typically demonstrates airflow limitation (obstructive pattern) with a drop in FEV1.

Other forms of lung transplant rejection include:

- Hyperacute rejection usually occurs on the first day of transplantation and is caused by preformed host antibodies against donor ABO or human leukocyte antigens (major histocompatibility complexes). Histology generally shows fibrinoid necrosis with hemorrhage and ischemia ("white graft" reaction).

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- Hyperacute rejection usually occurs on the first day of transplantation and is caused by preformed host antibodies against donor ABO or human leukocyte antigens (major histocompatibility complexes). Histology generally shows fibrinoid necrosis with hemorrhage and ischemia ("white graft" reaction).
- Acute rejection normally occurs within 6 months of transplantation and is typically caused by a cell-mediated immune response to donor human leukocyte antigens. Histology generally shows perivascular mononuclear infiltrates in the small blood vessels of the lung, which can expand to include the alveolar walls **(Choices A and E)**.

(Choice B) BOS can occasionally cause large airway scarring, leading to bronchiectasis, but this is not the primary pathologic manifestation.

(Choice C) Restrictive allograft syndrome, a less common type of chronic lung transplant rejection, can result in fibrotic changes to the pleurae. However, pulmonary function tests would reveal a restrictive (reduced FVC), not obstructive, pattern.

Educational objective:
Chronic lung transplant rejection is due primarily to progressive scarring of the small airways, leading to bronchiolitis obliterans. Manifestations occur months or years after transplantation and include obstructive lung disease (eg, reduced FEV1) with dyspnea and dry cough.

References

- Chronic lung allograft dysfunction phenotypes and treatment.
- Immunobiology of chronic lung allograft dysfunction: new insights from the bench and beyond.

or pops, and spirometry typically demonstrates airflow limitation (obstructive pattern) with a drop in FEV1.

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References

- Chronic lung allograft dysfunction phenotypes and treatment.
- Immunobiology of chronic lung allograft dysfunction: new insights from the bench and beyond.
- Current views on chronic rejection after lung transplantation.

Immunology	Pulmonary & Critical Care	Lung transplantation
Subject	System	Topic

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A 3-year-old boy experiences recurrent sinusitis and an episode of severe pneumonia. As part of his evaluation, *Candida* extract is injected intradermally. Forty-eight hours later, he returns to the clinic with a firm nodule measuring 16 mm in diameter where the extract was injected. Which of the following cell types is most likely responsible for the reaction observed in this patient?

A. B lymphocytes
B. Eosinophils
C. Mast cells
D. Neutrophils
E. T lymphocytes

Submit

A 3-year-old boy experiences recurrent sinusitis and an episode of severe pneumonia. As part of his evaluation, *Candida* extract is injected intradermally. Forty-eight hours later, he returns to the clinic with a firm nodule measuring 16 mm in diameter where the extract was injected. Which of the following cell types is most likely responsible for the reaction observed in this patient?

- A. B lymphocytes (4%)
- B. Eosinophils (2%)
- C. Mast cells (4%)
- D. Neutrophils (8%)
- ✓ E. T lymphocytes (80%)

Omitted
Correct answer
E

80%
Answered correctly

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Time Spent

03/30/2020
Last Updated

Explanation

This patient with recurrent infection is undergoing a delayed-type hypersensitivity **skin test** to screen for **cellular immunodeficiency**. This procedure involves intradermal injection of an antigen to which the patient has already been exposed (ie, *Candida* extract). Development of an area of induration (ie, tissue firmness) surrounding the injection site indicates a positive response and demonstrates effective cellular immunity. Skin testing can also be used as a control in patients with suspected tuberculosis exposure to ensure that the lack of response is not caused by anergy.

Contact dermatitis, granulomatous inflammation, and reactive skin testing (eg, tuberculin skin test, *Candida* extract skin reaction) are all examples

This patient with recurrent infection is undergoing a delayed-type hypersensitivity **skin test** to screen for **cellular immunodeficiency**. This procedure involves intradermal injection of an antigen to which the patient has already been exposed (ie, *Candida* extract). Development of an area of induration (ie, tissue firmness) surrounding the injection site indicates a positive response and demonstrates effective cellular immunity. Skin testing can also be used as a control in patients with suspected tuberculosis exposure to ensure that the lack of response is not caused by anergy.

Contact dermatitis, granulomatous inflammation, and reactive skin testing (eg, tuberculin skin test, *Candida* extract skin reaction) are all examples of **type IV** (T Cell–mediated) **delayed-type hypersensitivity** reactions. When reexposed to an antigen, previously sensitized **T lymphocytes** proliferate and release inflammatory cytokines that promote cell-mediated cytotoxicity ($CD8^+$ T cells) and/or macrophage recruitment and activation. The resulting tissue damage and swelling is typically evident **24-48 hours** after exposure.

(Choice A) Antibody production by activated B lymphocytes (eg, plasma cells) plays a central role in type I, II, and III hypersensitivity reactions. The timeframe of these reactions can be immediate (type I: eg, anaphylaxis, allergies) or variable (types II and III: eg, most autoimmune disorders, serum sickness).

(Choice B) Eosinophils are phagocytic cells that play a role in the defense against parasitic organisms. These cells are present in small numbers in the bloodstream but are often found in increased numbers in the affected tissues of patients with type I hypersensitivity responses (eg, asthma, allergies).

(Choice C) Mast cells are granulocytes that are the primary mediators of type I (immediate) hypersensitivity reactions (eg, allergies). Sensitized mast cells degranulate and release inflammatory mediators (eg, histamine, prostaglandins) when allergen-specific IgE cross-link on the mast cell Fc receptors, causing rapid swelling and tissue damage.

(Choice D) Neutrophils are the primary phagocytes of the innate immune system and play an ancillary role in some hypersensitivity reactions. Neutrophil deficiency or dysfunction can lead to severe infections without evidence of a significant immune response (eg, pus, infiltrates, erythema).

Educational objective:
Type IV (delayed) hypersensitivity reactions (eg, *Candida* extract skin test, contact dermatitis) are characterized by erythema and induration that

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Educational objective:
Type IV (delayed) hypersensitivity reactions (eg, *Candida* extract skin test, contact dermatitis) are characterized by erythema and induration that develops 24-48 hours after repeat exposure to an antigen. T lymphocytes mediate the inflammation in these reactions through cytokine release, $CD8^+$ cytotoxicity, and macrophage recruitment.

Immunology	Pulmonary & Critical Care	Hypersensitivity reactions
Subject	System	Topic

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Contact dermatitis, granulomatous inflammation, and reactive skin testing (eg, tuberculin skin test, *Candida* extract skin reaction) are all examples

Exhibit Display

Hypersensitivity reactions		
	Immunology	Examples
Type I (immediate)	IgE-mediated	• Anaphylaxis • Urticaria
Type II (cytotoxic)	IgG & IgM autoantibody-mediated	• Autoimmune hemolytic anemia • Goodpasture syndrome
Type III (immune complex)	Antibody-antigen complex deposition	• Serum sickness • Poststreptococcal glomerulonephritis • Lupus nephritis
Type IV (delayed type)	T cell- & macrophage-mediated	• Contact dermatitis • Tuberculin skin test

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A 14-year-old boy is brought to the emergency department by his mother after he develops a sudden rash. He was trying to retrieve a baseball that had rolled under a log when he got stung by something. By the time he told his mom, his body was covered in welts. His mother gave him diphenhydramine, but the patient's face started to swell and he was having a hard time swallowing. The patient's blood pressure is 70/50 mm Hg and heart rate is 120/min. Physical examination shows erythematous, raised plaques over the trunk, extremities, and face. Lung auscultation reveals bilateral expiratory wheezes. The mother is not aware of the child having any similar reaction in the past. Which of the following most likely triggered this patient's condition?

A. Antibody-antigen complex deposition in the endothelium

B. Antibody-dependent cell-mediated cytotoxicity

C. CD8+ T lymphocyte-mediated hypersensitivity

D. Cell surface-bound antibody bridging by antigen

E. Complement-mediated cytotoxicity

Submit

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- A. Antibody-antigen complex deposition in the endothelium (3%)
- B. Antibody-dependent cell-mediated cytotoxicity (9%)
- C. CD8+ T lymphocyte-mediated hypersensitivity (8%)
- ✓ D. Cell surface-bound antibody bridging by antigen (73%)
- E. Complement-mediated cytotoxicity (4%)

Omitted
Correct answer
D

73%
Answered correctly

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Time Spent

06/29/2020
Last Updated

Explanation

Hypersensitivity reactions			
	Humoral	Cellular	Examples

Hypersensitivity reactions			
	Humoral components	**Cellular components**	**Examples**
Type I (immediate)	• **IgE**	• Basophils • Mast cells	• Anaphylaxis • Allergies
Type II (cytotoxic)	• **IgG & IgM** autoantibodies • Complement activation	• NK cells • Eosinophils • Neutrophils • Macrophages	• Autoimmune hemolytic anemia • Goodpasture syndrome
Type III (immune complex)	• Deposition of **antibody-antigen complexes** • Complement activation	• Neutrophils	• Serum sickness • PSGN • Lupus nephritis
Type IV (delayed type)	• None	• **T cells** • **Macrophages**	• Contact dermatitis • Tuberculin skin test

NK = natural killer; **PSGN** = poststreptococcal glomerulonephritis.

This patient is experiencing **anaphylaxis**, a type I (immediate) hypersensitivity reaction that occurs in response to allergen (eg, venom from insect sting) exposure. An allergen is an antigen that promotes a robust immune response only in a subset of the population.

On initial exposure to allergen, a patient who will eventually develop an allergic response will undergo antibody class switching to **IgE** in B lymphocytes specific for these allergens. Antigen-specific IgE produced by plasma cells binds to IgE receptors on basophils in the blood and mast cells in the tissues. When the relevant antigen (allergen) interacts with cell bound-specific IgE, these antibodies will cross-link, causing

This patient is experiencing **anaphylaxis**, a type I (immediate) hypersensitivity reaction that occurs in response to allergen (eg, venom from insect sting) exposure. An allergen is an antigen that promotes a robust immune response only in a subset of the population.

On initial exposure to allergen, a patient who will eventually develop an allergic response will undergo antibody class switching to **IgE** in B lymphocytes specific for these allergens. Antigen-specific IgE produced by plasma cells binds to IgE receptors on basophils in the blood and mast cells in the tissues. When the relevant antigen (allergen) interacts with cell bound-specific IgE, these antibodies will cross-link, causing degranulation and release of chemical mediators (histamine, prostaglandin, leukotrienes) responsible for systemic vasodilation, increased vascular permeability, bronchoconstriction, and hemodynamic instability.

(Choice A) Antibody-antigen complex deposition in the vasculature occurs with Type III hypersensitivity reactions (eg, serum sickness, Arthus reaction).

(Choice B) Antibody-dependent cell-mediated cytotoxicity occurs in type II hypersensitivity reactions wherein IgM or IgG binds to antigens expressed on the cell surface. These antibodies are then recognized by Fc receptors on immune cells, triggering the release of perforin and granzymes that ultimately leads to cell lysis and death.

(Choice C) CD8+ T lymphocyte-mediated hypersensitivity is a delayed rather than immediate type of immune response. Type IV hypersensitivity is unique in that it is cell- versus antibody-mediated (seen in types I-III).

(Choice E) Complement-mediated cytotoxicity is a function of circulating IgM and IgG, not IgE. This pathway plays a role in the damage associated with Type II and III hypersensitivity reactions. IgM is the antibody most efficient at initiating the classical complement cascade because it circulates as a pentamer (allows for increased complement interaction).

Educational objective:
Type I hypersensitivity reactions are mediated by the interaction of allergen with preexisting IgE bound to basophils and mast cells. This facilitates cross-linking of the surface IgE molecules that signals the cell to degranulate releasing chemical mediators (eg, histamine, heparin). These agents are responsible for the immediate signs and symptoms of allergy, from a local wheal and flare to life-threatening anaphylaxis.

Immunology	Pulmonary & Critical Care	Anaphylaxis
Subject	System	Topic

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A 2-year-old boy is evaluated for recurrent infections. He was born at term after a normal pregnancy. His mother states, "He is always sick with something and is constantly on antibiotics." The patient's past medical records indicate multiple episodes of otitis media, skin infections, and pneumonia. Incision and drainage of his skin infections revealed *Staphylococcus aureus* on bacterial culture but no purulence. His infections usually resolve with prolonged antibiotic courses. Laboratory testing reveals absent CD18 antigens on the surface of leukocytes. The patient is at greatest risk for which of the following?

A. Infection following live-virus vaccines

B. Infection with *Neisseria*

C. Persistent leukocytosis

D. Small or absent lymph nodes

E. Thrombocytopenia and eczema

Submit

A 2-year-old boy is evaluated for recurrent infections. He was born at term after a normal pregnancy. His mother states, "He is always sick with something and is constantly on antibiotics." The patient's past medical records indicate multiple episodes of otitis media, skin infections, and pneumonia. Incision and drainage of his skin infections revealed *Staphylococcus aureus* on bacterial culture but no purulence. His infections usually resolve with prolonged antibiotic courses. Laboratory testing reveals absent CD18 antigens on the surface of leukocytes. The patient is at greatest risk for which of the following?

- A. Infection following live-virus vaccines (11%)
- B. Infection with *Neisseria* (18%)
- ✓ C. Persistent leukocytosis (51%)
- D. Small or absent lymph nodes (10%)
- E. Thrombocytopenia and eczema (8%)

Omitted
Correct answer
C

51%
Answered correctly

01 sec
Time Spent

03/15/2020
Last Updated

Explanation

Features of leukocyte adhesion deficiency
• Recurrent skin & mucosal bacterial infections (eg, omphalitis,

Explanation

Features of leukocyte adhesion deficiency

- Recurrent skin & mucosal bacterial infections (eg, omphalitis, periodontitis)
  - No pus (lack of neutrophils at inflammation site)
  - Poor wound healing
- Delayed umbilical cord separation (>21 days)
- Marked peripheral leukocytosis with neutrophilia

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This patient's recurring skin and mucosal infections as well as absence of purulence are highly suggestive of **leukocyte adhesion deficiency** (LAD). LAD is an autosomal recessive disorder characterized by **absence of CD18** antigens, which are necessary for the formation of integrins. Integrins are essential for leukocyte adhesion to endothelial surfaces and migration to peripheral tissues in response to infection or inflammation.

The failure of leukocyte chemotaxis results in LAD findings, which include recurrent skin and mucosal infections (often due to *Staphylococcus aureus* or gram-negative rods) and periodontal disease. LAD-related infections are notable for **lack of purulence** due to absence of leukocytes in peripheral tissues. Wound healing is also impaired, including **late separation** (>21 days) of the umbilical cord. **Persistent leukocytosis** is a common finding due to leukocytes not being able to migrate out of the blood vessels.

(Choice A) Deficiencies of T cell-mediated immunity (eg, HIV infection, severe combined immune deficiency) are associated with infection following live vaccines. However, LAD does not impair response to live vaccines.

(Choice B) Deficiency of the terminal complement components (C5b-C9) results in an inability to form the complement membrane attack complex. This condition predisposes to recurrent infections by *Neisseria* organisms.

(Choice D) The absence of B lymphocytes in X-linked agammaglobulinemia leads to hypoplasia of lymphoid tissue, such as the tonsils or lymph nodes. However, both B cell number and function are normal in LAD.

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(Choice D) The absence of B lymphocytes in X-linked agammaglobulinemia leads to hypoplasia of lymphoid tissue, such as the tonsils or lymph nodes. However, both B cell number and function are normal in LAD.

(Choice E) Wiskott-Aldrich syndrome is an X-linked disorder characterized by the triad of thrombocytopenia, immunodeficiency, and eczema. It is caused by a defect in cytoskeleton rearrangement, not by CD18 deficiency.

Educational objective:
Leukocyte adhesion deficiency is due to absence of CD18 antigens necessary for the formation of integrins. Clinical features are caused by failure of leukocyte chemotaxis and include recurrent skin and mucosal infections without purulence, delayed separation of the umbilical cord, and persistent leukocytosis.

References

- Disorders of neutrophil function: an overview.
- Leukocyte adhesion deficiencies.
- Defects of the leukocyte adhesion cascade

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References

- Disorders of neutrophil function: an overview.
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- Defects of the leukocyte adhesion cascade.

Immunology	Rheumatology/Orthopedics & Sports	Primary immunodeficiency disorder
Subject	System	Topic

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A 23-year-old woman is brought to the emergency department due to one day of fever, vomiting, diarrhea, and muscle pains. The symptoms developed rapidly over the course of the day. The patient is confused and unable to answer questions. She has no known medical problems and takes no medications. She lives with her boyfriend. The patient's temperature is 39.1 C (102.4 F), blood pressure is 88/50 mm Hg, pulse is 120/min, and respirations are 20/min. A diffuse, erythematous, macular rash resembling a sunburn is noted on dermatologic examination; pelvic examination reveals a tampon in the vagina. Laboratory results are as follows:

Leukocytes	8,000/mm^3
Creatinine	1.4 mg/dL
Aspartate aminotransferase (SGOT)	62 U/L
Alanine aminotransferase (SGPT)	49 U/L

A pregnancy test is negative. Activation of which of the following cells is most likely primarily responsible for this patient's condition?

- A. Basophils and macrophages
- B. Macrophages and T lymphocytes
- C. Mast cells and eosinophils
- D. Neutrophils and B lymphocytes
- E. Platelets and mast cells

Submit

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A pregnancy test is negative. Activation of which of the following cells is most likely primarily responsible for this patient's condition?

- A. Basophils and macrophages (3%)
- ✓ B. Macrophages and T lymphocytes (67%)
- C. Mast cells and eosinophils (11%)
- D. Neutrophils and B lymphocytes (12%)
- E. Platelets and mast cells (5%)

Omitted
Correct answer
B

67%
Answered correctly

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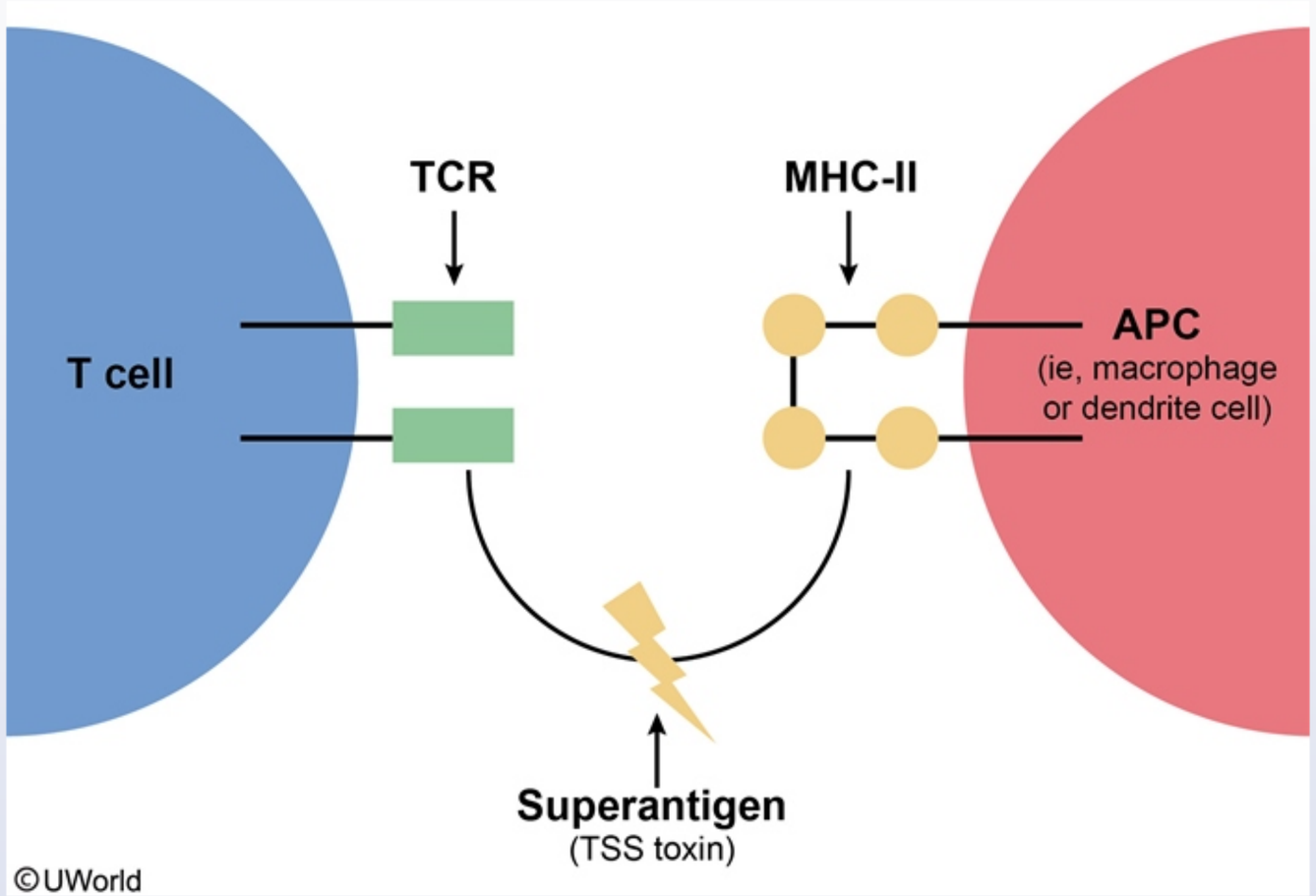

Fever, vomiting, diarrhea, muscle pains, and erythroderma (diffuse macular rash resembling a sunburn) are manifestations of **toxic shock syndrome (TSS)**. TSS can rapidly progress to severe hypotension and multisystem dysfunction (eg, elevated creatinine, elevated transaminases). Desquamation, particularly on the palms and soles, can occur 1-2 weeks after the onset of illness. TSS has been associated with the use of **tampons** and nasal packing.

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Staphylococcus aureus strains producing **toxic shock syndrome toxin** (TSST) are responsible for most cases of TSS. TSST acts as a **superantigen** that activates large numbers of helper T cells (compared to a regular antigen, which activates few helper T cells). Superantigens interact with major histocompatibility complex molecules on antigen-presenting cells (eg, **macrophages**) and with the variable region of the **T lymphocyte** receptor to cause a nonspecific, **widespread** activation of T lymphocytes. Activation of T cells is responsible for the release of interleukin (IL)-2 from the T cells and IL-1 and tumor necrosis factor from macrophages. These ILs cause capillary leakage, circulatory collapse, hypotension, shock, fever, skin findings, and multiorgan failure.

(Choice A) Basophils are not involved in TSS. Basophilia can be seen with some myeloproliferative disorders and, rarely, certain parasitic infections.

(Choices C and E) Eosinophil activation is associated with reactions to allergens and parasites, hypersensitivity reactions to drugs, and some hematologic malignancies. Mast cells, when stimulated (due to antigen-induced cross-linking of IgE on their cell membrane), release histamine, prostaglandins, leukotrienes, and other inflammatory mediators; they are active in allergic reactions and anaphylaxis.

(Choice D) B lymphocytes respond to activation by replicating and synthesizing antibodies specific for the antigen with which they were presented; they are not responsible for TSS. Neutrophilia is commonly seen with TSS.

Educational objective:
Superantigens (eg, toxic shock syndrome toxin) interact with major histocompatibility complex molecules on antigen-presenting cells and the variable region of the T lymphocyte receptor to cause nonspecific, widespread activation of T cells. This results in the release of interleukin (IL)-2 from the T cells and IL-1 and tumor necrosis factor from macrophages. This immune cascade is responsible for the manifestations of toxic shock syndrome.

Immunology	Infectious Diseases	Toxic shock syndrome
Subject	System	Topic

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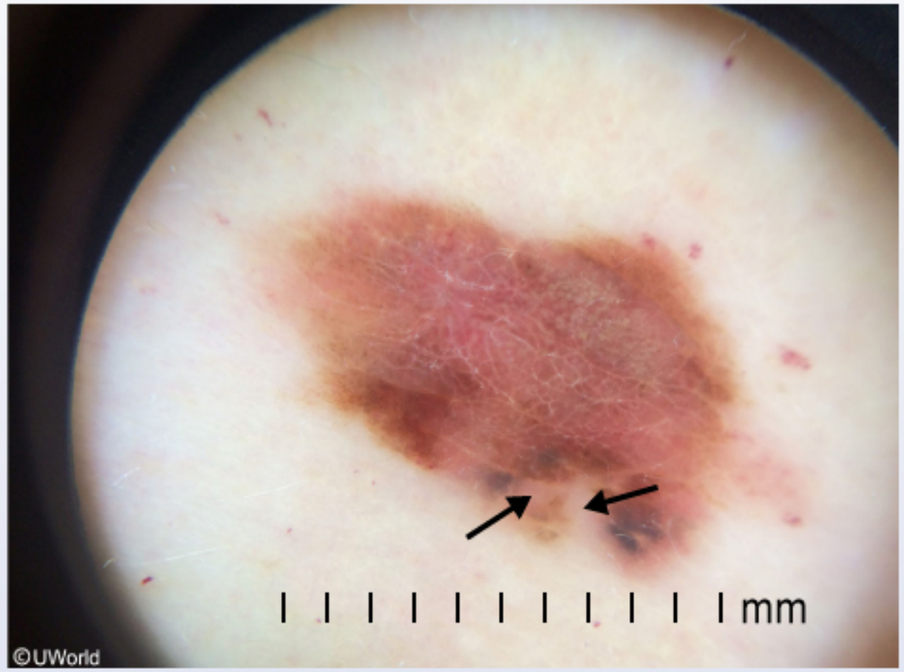
A 50-year-old woman comes to the office for evaluation of a mole on her back. The mole has been present for several years, but her daughter is concerned that it might have grown larger lately. The patient has no other medical conditions but had frequent sunburns during childhood. Dermoscopic examination of the lesion is shown in the image below.



The lesion has multiple color variations, including dark brown, pink, red, and whitish areas. Excisional biopsy of the lesion is performed. The whitish areas (arrows) seen on histologic examination most likely represent which of the following underlying processes?

A. Intense inflammation

B. Melanocyte regression

C. Proliferating, neoplastic melanocytes

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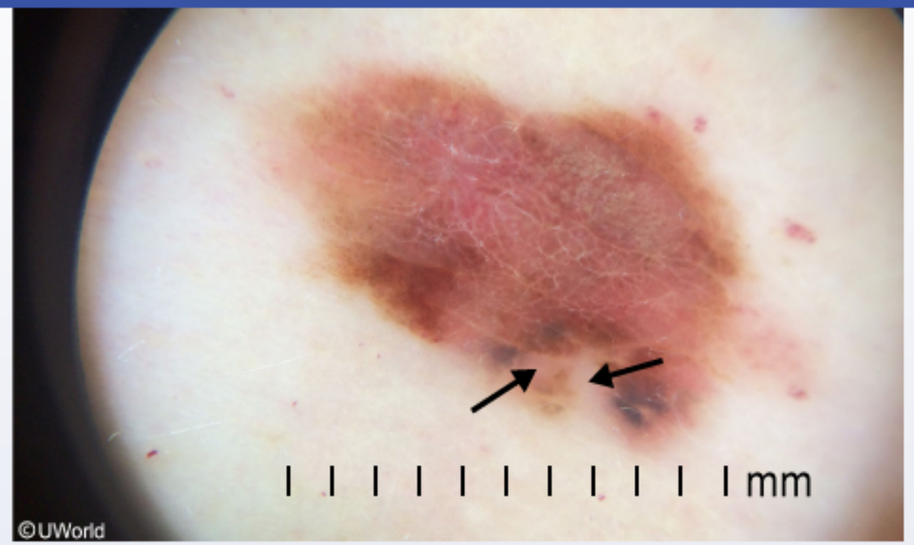

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- A. Intense inflammation
- B. Melanocyte regression
- C. Proliferating, neoplastic melanocytes
- D. Proliferating, nonneoplastic melanocytes
- E. Vessel ectasia

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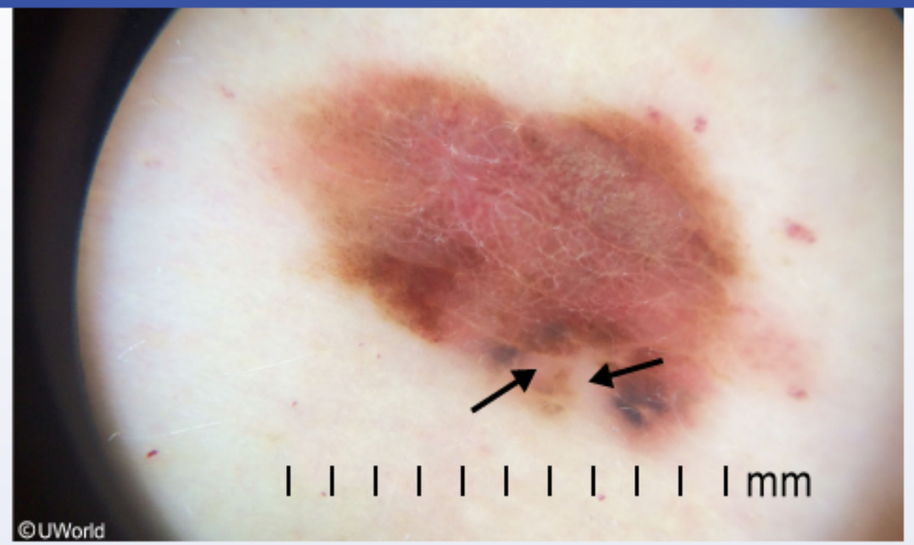

The lesion has multiple color variations, including dark brown, pink, red, and whitish areas. Excisional biopsy of the lesion is performed. The whitish areas (arrows) seen on histologic examination most likely represent which of the following underlying processes?

- A. Intense inflammation (3%)
- ✓ B. Melanocyte regression (43%)
- C. Proliferating, neoplastic melanocytes (31%)
- D. Proliferating, nonneoplastic melanocytes (9%)
- E. Vessel ectasia (10%)

Omitted
Correct answer

43%
Answered correctly

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Explanation

This patient who had multiple sunburns as a child has a skin lesion with several classic features of **melanoma**, including **A**symmetry, **B**order irregularity, **C**olor variegation, **D**iameter ≥6 mm (hash marks), and **E**volution over time.

Color variegation is a common feature of melanoma; the different colors represent different areas of activity within the tumor:

- Red areas are due to vessel ectasia (dilation) and local inflammation **(Choices A and E)**.
- Brown or black, flared areas along the border are due to advancing, neoplastic melanocytes **(Choice C)**.
- White and gray areas appear when **cytotoxic T lymphocytes** recognize tumor antigens (eg, melan-A) and induce apoptosis, leading to malignant **melanocyte regression** (cleared patches).

Melanocyte regression is also a hallmark of treatment response to melanoma immunotherapies, such as the programmed cell death receptor-1 (**PD-1**) **inhibitor** pembrolizumab.

(Choice D) This patient's skin findings are characteristic of malignant melanoma. Proliferating nonneoplastic melanocytes do not generally play a role in the development or progression of melanoma.

Educational objective:
Melanoma lesions often have multiple color variations. The different colors represent different activities within the tumor. Whitish/gray areas occur when cytotoxic T cells recognize tumor antigens and destroy malignant cells, leading to melanocyte regression. Red areas arise due to vessel ectasia and local inflammation, whereas brown or black areas are generally due to advancing malignant melanocytes.

Immunology	Dermatology	Melanoma
Subject	System	Topic

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A 67-year-old man comes to the office after he noticed several nodules in his left axilla. He has a history of malignant melanoma on his upper back, which was treated with wide surgical excision 4 years ago. The patient undergoes biopsy of an axillary lesion, and histopathology reveals melanoma recurrence. Subsequent whole-body positron emission scan shows diffuse metastatic disease involving the lungs, liver, and left axillary nodes. Checkpoint inhibitor therapy with pembrolizumab is initiated, which leads to significant reduction in the size of the axillary nodules and metastatic lesions. Which of the following best correlates with the treatment response in this patient?

- A. Increased intratumor macrophages
- B. Intense desmoplastic reaction
- C. Ischemic tumor necrosis
- D. CD8+ lymphocyte infiltration
- E. Peritumoral neutrophilic reaction

Submit

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- A. Increased intratumor macrophages (12%)
- B. Intense desmoplastic reaction (8%)
- C. Ischemic tumor necrosis (16%)
- ✓ D. CD8+ lymphocyte infiltration (57%)
- E. Peritumoral neutrophilic reaction (5%)

Omitted
Correct answer
D

57%
Answered correctly

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Explanation

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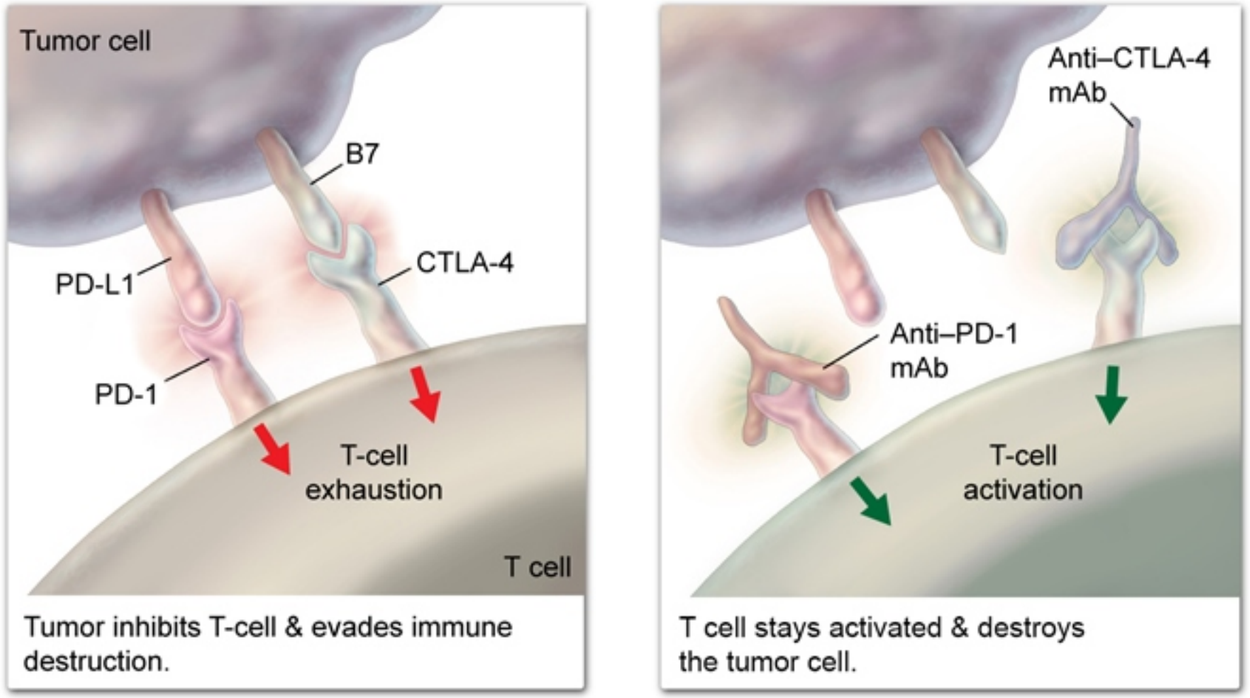
Cancer immunotherapy: anti–PD-1 & anti–CTLA-4 antibodies



CTLA-4 = cytotoxic T-lymphocyte–associated protein 4; **mAb** = monoclonal antibody;
PD-1 = programmed death receptor-1; **PD-L1** = programmed death ligand-1.
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Neoplastic cells produce proteins not found in healthy cells. Pieces of these proteins **(neoantigens)** are displayed on MHC class I molecules on the cell surface and are subsequently recognized by **cytotoxic T cells** as "nonself" (leading to cellular apoptosis). However, neoplastic cells generally accumulate genetic mutations that allow them to thwart the cytotoxic T-cell response and evade detection/destruction. One common mechanism is the overexpression of **programmed death-ligand 1** (PD-L1) on the cancer cell surface; this ligand binds to the PD-1 receptor on cytotoxic T cells and suppresses their ability to induce apoptosis (**T-cell exhaustion**).

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Treatment with monoclonal antibodies that block PD-1 such as **pembrolizumab** have shown promise in cancers that overexpress PD-L1 (eg, **melanoma**, renal cell carcinoma). **Blockade of PD-1** restores the cytotoxic T-cell response (disinhibition), which **promotes tumor cell apoptosis**. Patients with advanced melanoma and other susceptible malignancies often have a drastic clinical response (eg, tumor regression, long-term remission) to PD-1 antagonists.

(Choices A and E) Cancer-related inflammation also involves cells of the innate immune system such as macrophages and neutrophils. These cells can have either protumor (eg, release of matrix metalloproteases that facilitate invasion) and antitumor (eg, direct killing of cancer cells) activities depending on the local cytokine milieu. However, PD-1 inhibitors do not increase the antitumor activity of neutrophils or macrophages.

(Choice B) Tumor cells often induce desmoplasia, which refers to excessive connective tissue/stroma growth around the tumor. A strong desmoplastic response can reduce the ability of chemotherapeutic agents to penetrate into the tumor, leading to chemoresistance.

(Choice C) Angiogenesis inhibitors (eg, bevacizumab) are used to prevent neovascularization of growing tumors, leading to ischemia and tumor necrosis. PD-1 inhibitors cause cytotoxic T-cell activation, leading to increased apoptosis of tumor cells; they do not induce ischemic necrosis.

Educational objective:
Programmed-death receptor 1 (PD-1) is a checkpoint inhibitor that downregulates the cytotoxic T-cell response. Neoplastic cells often exploit this receptor via the overexpression of PD-1 ligand. PD-1 receptor inhibitors (eg, Pembrolizumab) restore the T-cell response, allowing cytotoxic T cells to invade the tumor and induce apoptosis of neoplastic cells.

Immunology	Dermatology	Melanoma
Subject	System	Topic

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A 7-year-old boy is brought to the emergency department by his parents for abdominal pain and arthralgias. He had a cough and runny nose last week but otherwise has been in good health. The patient's temperature is 37 C (98.6 F), pulse is 92/min, and respirations are 20/min. Physical examination shows palpable purpura over his buttocks and thighs. Auscultation of the lungs and heart is normal. His abdomen is diffusely tender to palpation without rebound or guarding. Both knees are tender but do not appear warm or swollen. A stool occult blood test is positive. Urinalysis results are as follows:

Protein	2+
Blood	moderate
Leukocyte esterase	trace
Nitrites	negative
White blood cells	1-2/hpf
Red blood cells (RBCs)	many/hpf
Casts	RBC casts

Which of the following mechanisms is the most likely underlying cause of this patient's condition?

A. Antibody-dependent cellular cytotoxicity
B. Circulating immune complexes
C. Delayed hypersensitivity reaction
D. Disseminated bacterial infection
E. IgE-dependent degranulation

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Urinalysis results are as follows:

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Blood	moderate
Leukocyte esterase	trace
Nitrites	negative
White blood cells	1-2/hpf
Red blood cells (RBCs)	many/hpf
Casts	RBC casts

Which of the following mechanisms is the most likely underlying cause of this patient's condition?

A. Antibody-dependent cellular cytotoxicity (17%)
✓ B. Circulating immune complexes (75%)
C. Delayed hypersensitivity reaction (2%)
D. Disseminated bacterial infection (2%)
E. IgE-dependent degranulation (1%)

Omitted
Correct answer

75%
Answered correctly

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Explanation

Henoch-Schönlein purpura	
Pathogenesis	• **IgA immune complex**-mediated vasculitis • Generally follows upper respiratory or other minor infection
Clinical manifestations	• **Palpable purpura** • **Arthralgias** • **Abdominal pain**, intussusceptions • Renal disease similar to IgA nephropathy **(hematuria)**
Diagnosis	• Usually made clinically • Confirmed by skin biopsy showing **IgA deposition** in blood vessels

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This child has signs and symptoms consistent with **Henoch-Schönlein purpura (HSP)**, the most common systemic vasculitis in children. It predominantly affects those age 3-10 and often occurs following infection (eg, upper respiratory tract infection). HSP is caused by circulating **IgA-antigen immune complexes** (type III hypersensitivity reaction). Deposition of these complexes in the walls of **small vessels** and the **renal mesangium** leads to recruitment of neutrophils and lymphocytes as well as activation of complement via the alternate/lectin pathways. The resulting inflammation leads to the organ dysfunction and palpable purpura found in HSP. The condition is **self-limited** and resolves as the circulating immune complexes clear. Treatment is supportive unless specific complications (eg, intussusception) occur.

(Choice A) Antibody-dependent cellular cytotoxicity (type II hypersensitivity) is part of the body's defense against viral and parasitic infections. Antibodies bound to antigens on the surface of infected cells are recognized by the Fc receptors on effector cells (eg, natural killer cells

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(Choice A) Antibody-dependent cellular cytotoxicity (type II hypersensitivity) is part of the body's defense against viral and parasitic infections. Antibodies bound to antigens on the surface of infected cells are recognized by the Fc receptors on effector cells (eg, natural killer cells, neutrophils, eosinophils) that then destroy the infected cells by releasing cytolytic granules.

(Choice C) Delayed hypersensitivity reactions (type IV hypersensitivity) are T cell and macrophage-mediated responses. They occur in response to *Mycobacterium tuberculosis* infections and in certain allergic reactions, such as contact dermatitis and transplant rejection.

(Choice D) A palpable skin rash is commonly seen with disseminated *Neisseria* infections (meningococcemia or disseminated gonococcus). Unlike the purpura of HSP, which is generally limited to the lower extremities, the rash of disseminated *Neisseria* begins with petechiae on the trunk and spreads over the entire body. Patients also have fever, hypotension, and tachycardia.

(Choice E) IgE-dependent degranulation occurs in atopic and anaphylactic reactions (type I hypersensitivity). IgE on the surface of mast cells and basophils binds the offending allergen and triggers degranulation with release of histamine, serotonin, and other vasoactive substances.

Educational objective:
Henoch-Schönlein purpura is an IgA-mediated type III hypersensitivity reaction in children that generally follows infection. Deposition of circulating IgA-containing immune complexes in small vessels results in systemic vasculitis. Common manifestations include palpable lower-extremity purpura, abdominal pain, arthralgias, and hematuria.

References

- Henoch-Schönlein purpura nephritis.
- The role of secretory IgA and complement in IgA nephropathy.
- Activation of the lectin complement pathway in Henoch-Schönlein purpura nephritis.

This child has signs and symptoms consistent with **Henoch-Schönlein purpura (HSP)**, the most common systemic vasculitis in children. It

Exhibit Display

Henoch-Schonlein purpura Henoch-Schönlein purpura

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- Activation of the lectin complement pathway in Henoch-Schönlein purpura nephritis

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Exhibit Display

Henoch-Schonlein purpura Henoch-Schönlein purpura

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- Activation of the lectin complement pathway in Henoch-Schönlein purpura nephritis

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Immunology	Renal, Urinary Systems & Electrolytes	Henoch schonlein purpura
Subject	System	Topic

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A 44-year-old man with a chronic cough and progressive weight loss comes to the emergency department. He has lost 5 kg (11 lb) over the past 3 months. The patient recently emigrated from Southeast Asia. Temperature is 37.4 C (99.3 F), blood pressure is 113/70 mm Hg, pulse is 78/min, and respirations are 18/min. Chest x-ray reveals an apical left lung infiltrate. Sputum Gram stain and cultures are negative. However, lung biopsy culture grows acid-fast bacilli. Histology results are shown below.

The finding indicated by the arrow most likely resulted from which of the following?

A. Activation of CD8 T lymphocytes
B. B-lymphocyte transformation
C. Fibroblast proliferation
D. Neutrophil infiltration
E. Stimulation by CD4 T lymphocytes

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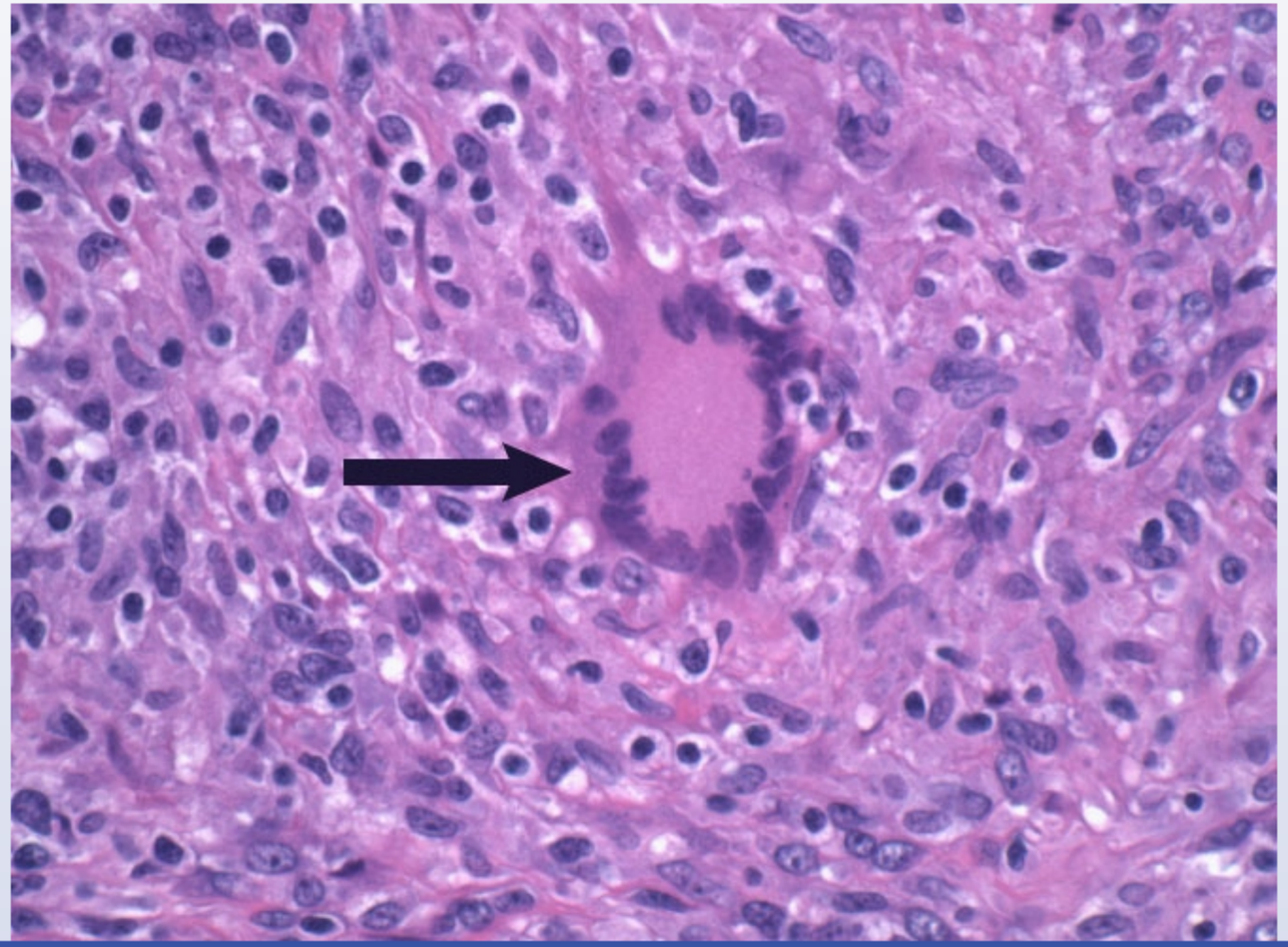

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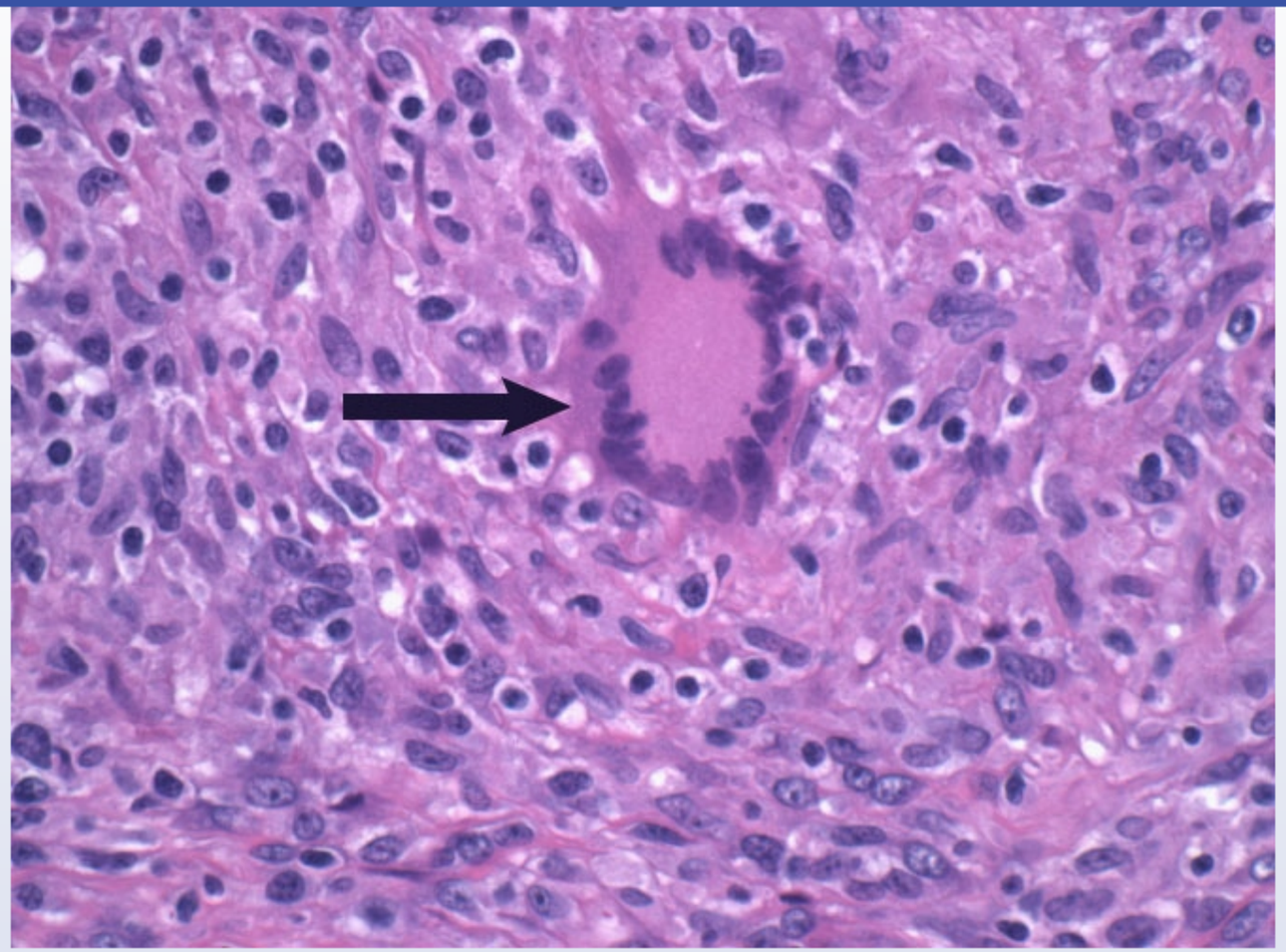

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A. Activation of CD8 T lymphocytes

B. B-lymphocyte transformation

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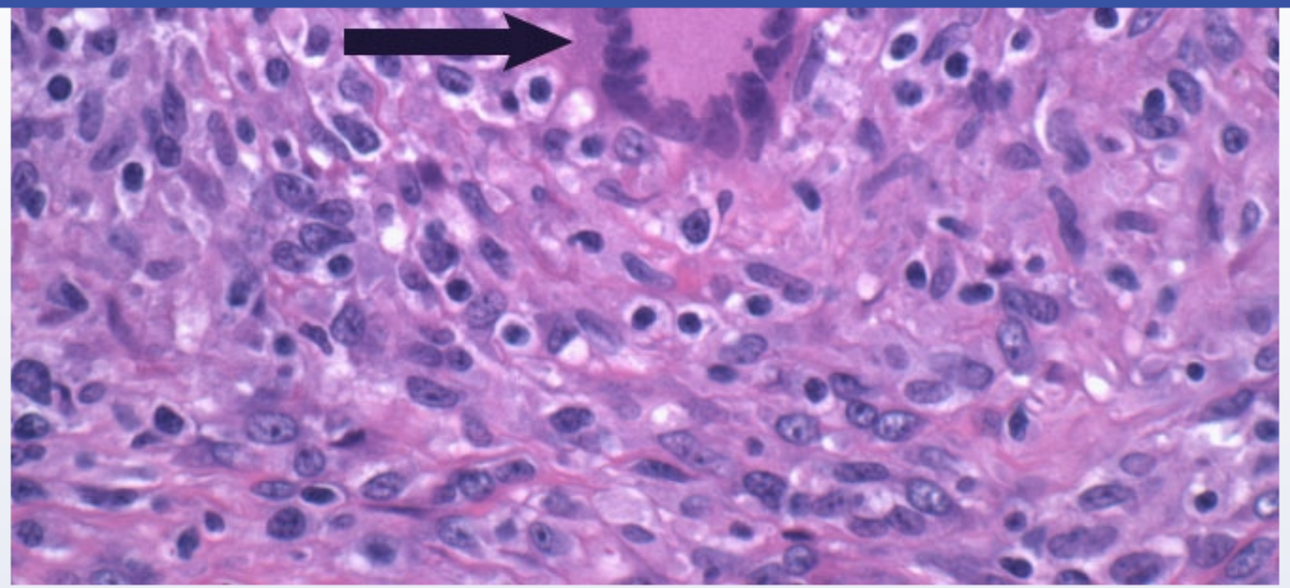

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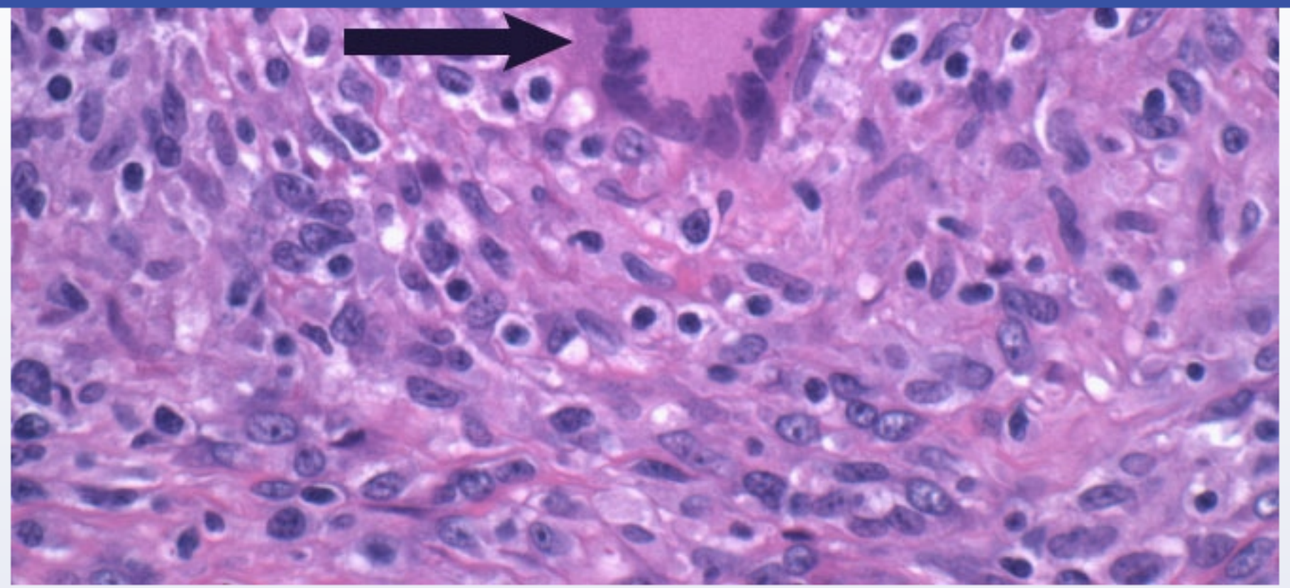

The finding indicated by the arrow most likely resulted from which of the following?

A. Activation of CD8 T lymphocytes (11%)

B. B-lymphocyte transformation (0%)

C. Fibroblast proliferation (4%)

D. Neutrophil infiltration (4%)

✓ E. Stimulation by CD4 T lymphocytes (78%)

Omitted
Correct answer

78%
Answered correctly

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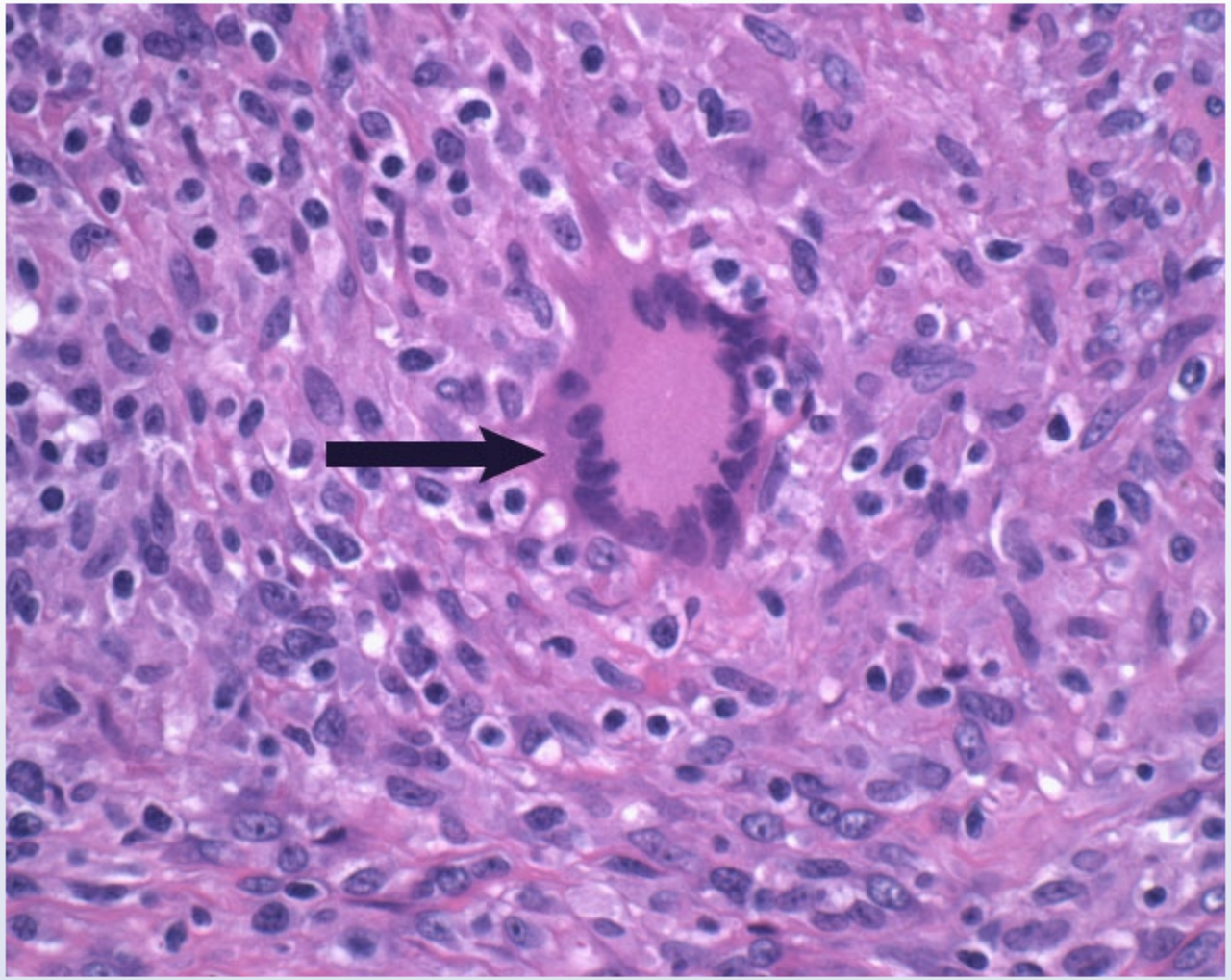

This patient from Southeast Asia has weight loss, cough, and an apical infiltrate with acid-fast bacilli, raising strong suspicion for **pulmonary tuberculosis**. *Mycobacterium tuberculosis* is transmitted to the lungs via aerosolized droplets. It initially replicates in an unchecked fashion within the alveoli and alveolar macrophages due to virulence factors (eg, cord factor) that prevent macrophage-mediated phagolysosome destruction.

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Stimulated CD4 cells release **interferon-gamma** that activates macrophages, greatly increasing their ability to kill phagocytized organisms. Activated macrophages can also differentiate into epithelioid histiocytes and coalesce into **multinucleated Langhans giant cells** (arrow in image) that wall off extracellular mycobacteria within granulomas. The center of the granuloma is acidic and hypoxic, which causes it to appear acellular, necrotic, and "cheese-like" (**caseating**). Granulomas typically limit mycobacterial proliferation but do not fully eliminate the infection.

Although Langhans giant cells are an important component of the immunologic response to pulmonary tuberculosis, they are a nonspecific finding that may also be present in other chronic infectious or inflammatory conditions (eg, sarcoidosis, Crohn disease).

(Choice A) Some intracellular bacterial pathogens (eg, *Listeria*, *Rickettsia*) have virulence factors that allow them to escape the phagosome and replicate within the cytosol. These pathogens are primarily processed by the proteasome (rather than the lysosome), leading to the display of bacterial protein fragments on MHC class I molecules. MHC class I molecules stimulate cytotoxic T cells (CD8 lymphocytes). In contrast, phagocytosed bacteria that remain within the phagosome (eg, *M tuberculosis*) are broken down by the lysosome and displayed on MHC class II molecules, which activate CD4, not CD8, cells.

(Choice B) Epstein-Barr virus attacks B lymphocytes and leads to long-term, latent infection that is typically asymptomatic but can occasionally lead to B-lymphocyte malignant transformation. Although malignant transformation can cause large, atypical cells, acid-fast bacilli would not be seen on culture.

(Choice C) Fibroblast proliferation and collagen production contribute to caseating granuloma formation but do not cause macrophage activation.

(Choice D) Neutrophils (polymorphonuclear cells) have multilobed nuclei that would be visible at this magnification. Neutrophils play a major role in early inflammation and elimination of extracellular bacterial pathogens (eg, *Staphylococcus aureus*). However, they are not the primary effector cell in the elimination of facultative intracellular pathogens such as *M tuberculosis*.

Educational objective:

Mycobacterium tuberculosis triggers CD4 T lymphocytes to release interferon-gamma, which leads to macrophage activation (improves

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Educational objective:

Mycobacterium tuberculosis triggers CD4 T lymphocytes to release interferon-gamma, which leads to macrophage activation (improves intracellular killing ability) and differentiation into epithelioid histiocytes. These cells, along with horseshoe-shaped, multinucleated Langhans giant cells (fused, activated macrophages) are a key component of granuloma formation.

References

- The tuberculous granuloma: an unsuccessful host defence mechanism providing a safety shelter for the bacteria?
- Granuloma with langhans giant cells: an overview.

Immunology	Pulmonary & Critical Care	Tuberculosis
Subject	System	Topic

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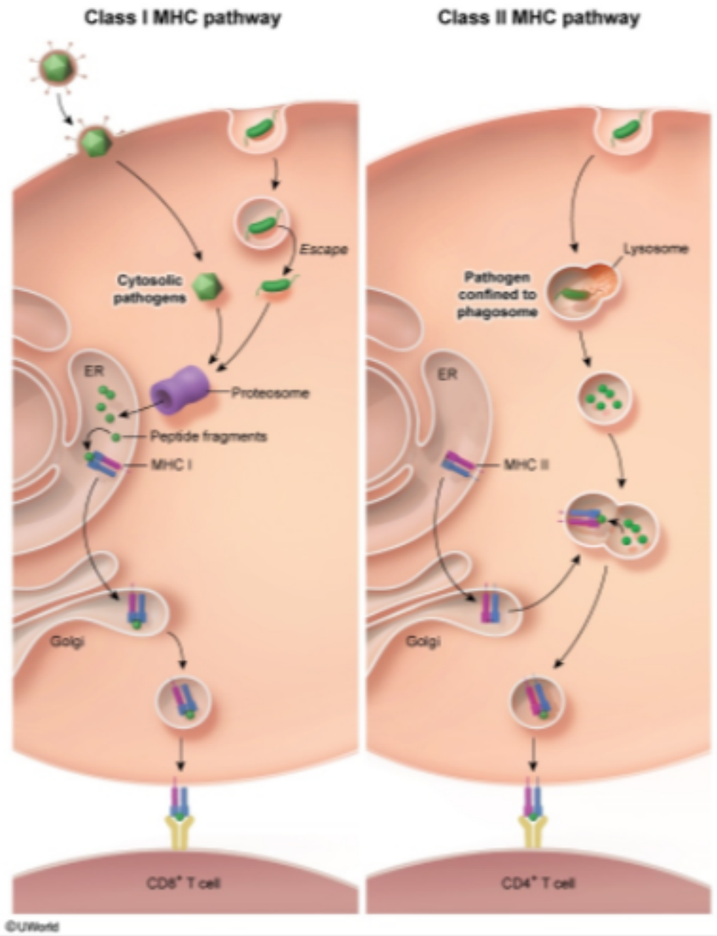

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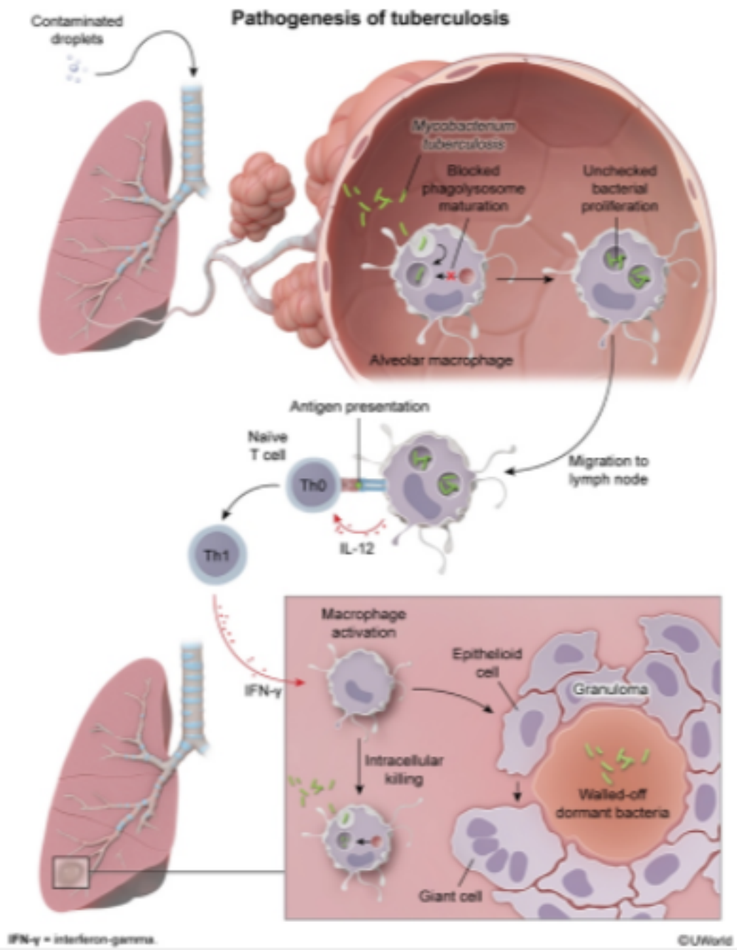

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Researchers develop a novel agent to treat extrinsic asthma. In a clinical trial, patients with moderate to severe asthma treated with this medication experience fewer exacerbations. They are found to have lower levels of serum IgE, even after exposure to triggering allergens. This medication helps improve asthma symptoms by binding and inhibiting the substance produced by sensitized Th2 cells in the airways that promotes immunoglobulin isotype switching in B lymphocytes. Which of the following is the most likely target of this medication?

A. Interleukin-1
B. Interleukin-3
C. Interleukin-4
D. Interleukin-5
E. Interferon-gamma
F. Transforming growth factor-beta

Submit

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- A. Interleukin-1 (1%)
- B. Interleukin-3 (3%)
- ✓ C. Interleukin-4 (72%)
- D. Interleukin-5 (15%)
- E. Interferon-gamma (4%)
- F. Transforming growth factor-beta (1%)

Omitted
Correct answer
C

72%
Answered correctly

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Explanation

Pathogenesis of asthma

Initial exposure

Repeat exposure

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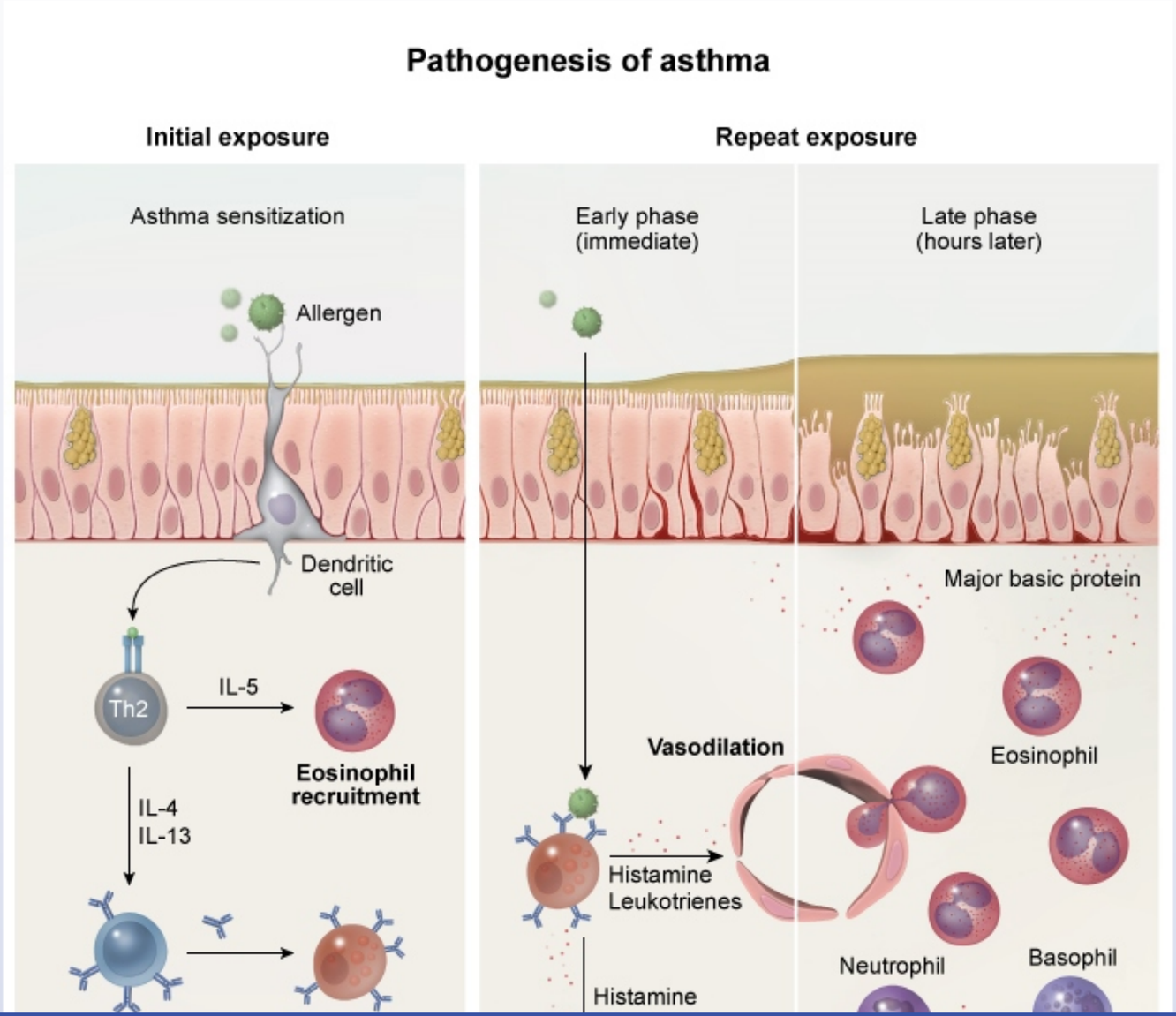

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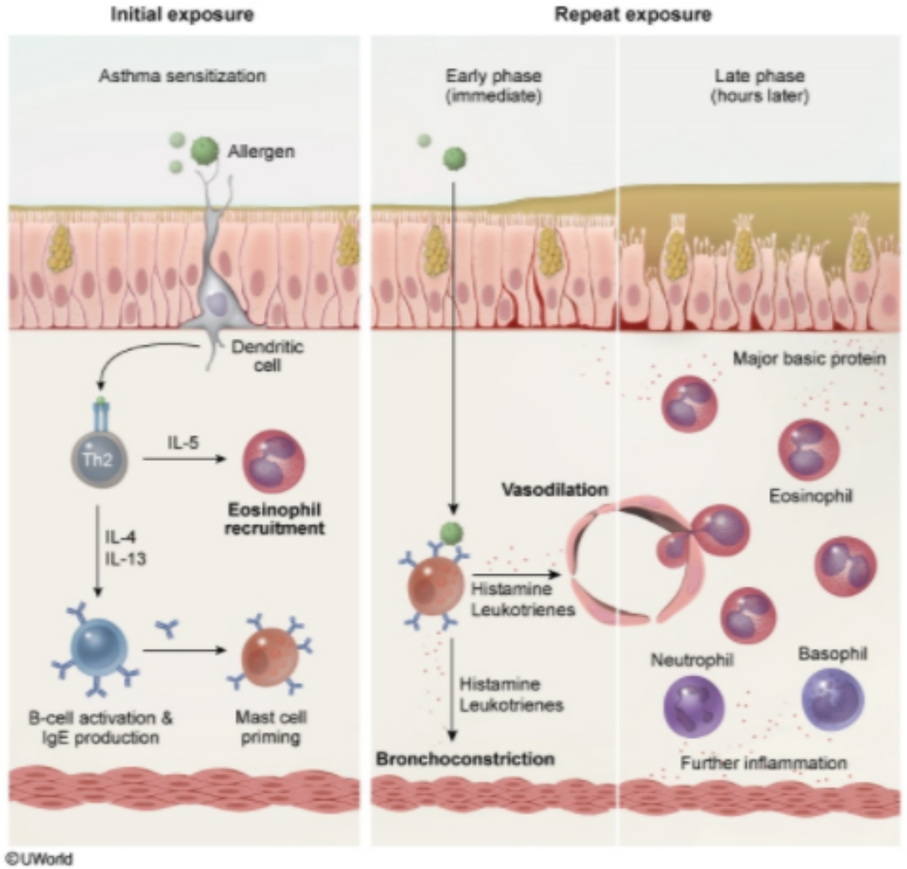
Pathogenesis of asthma



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Histamine

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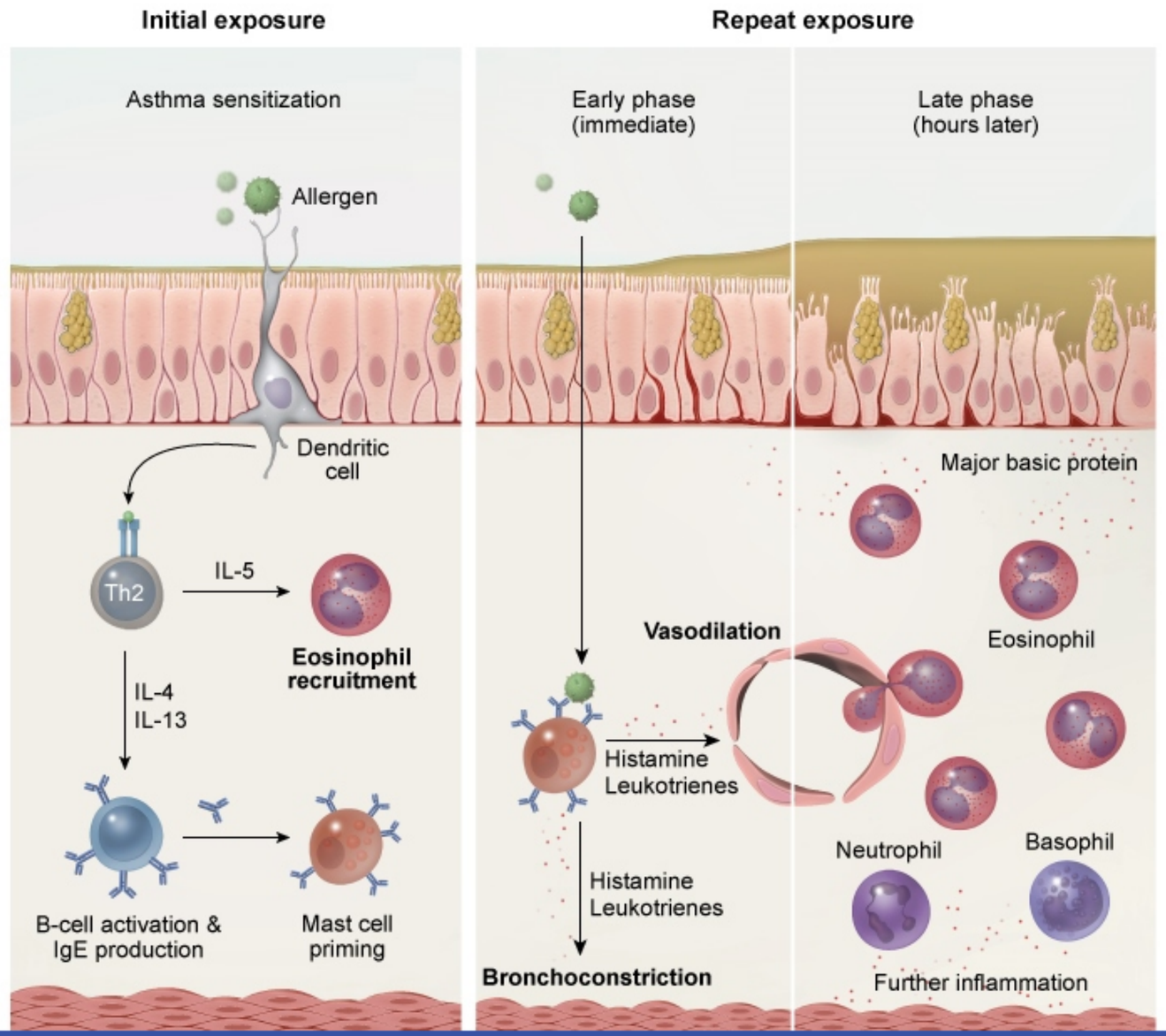

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Initial exposure
Repeat exposure

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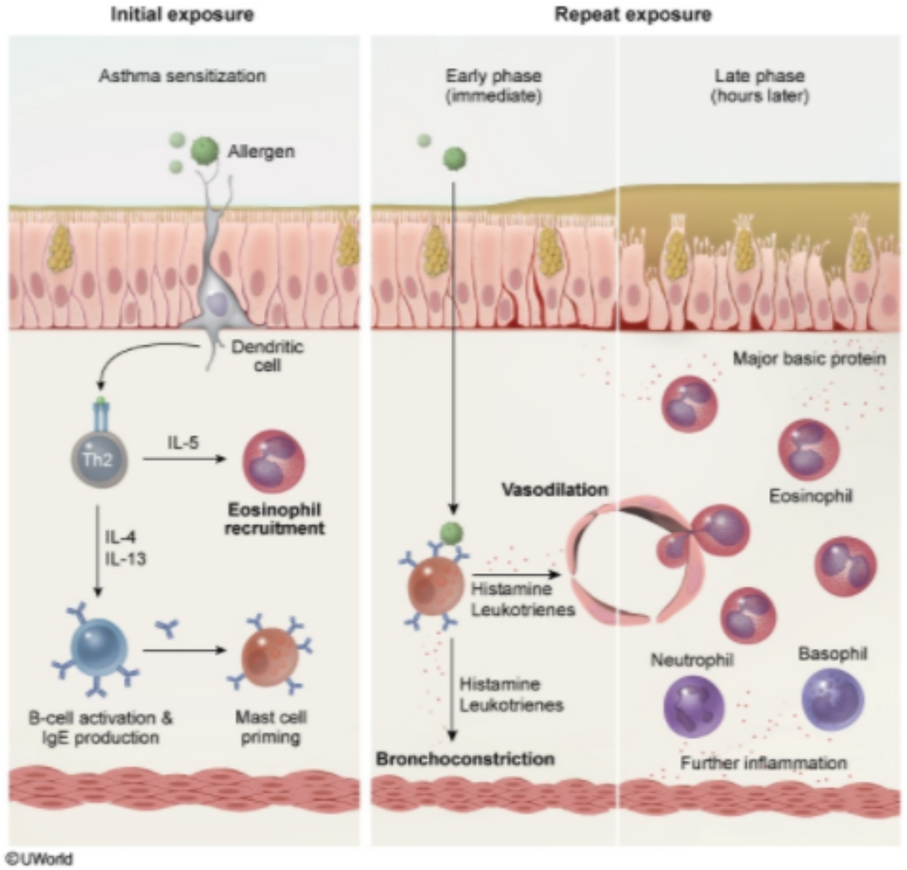
Pathogenesis of asthma



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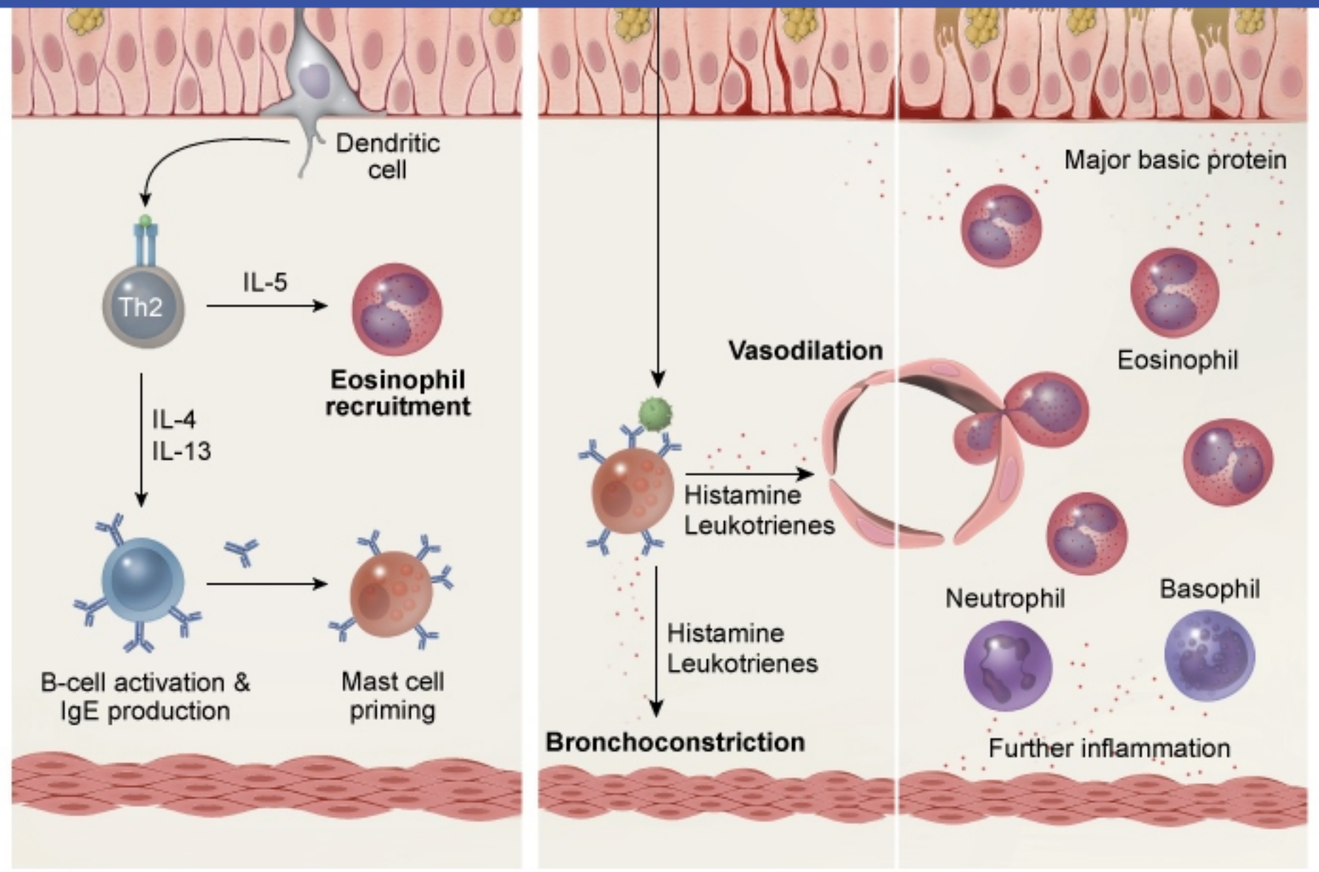

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There are 2 classes of CD4⁺ T-helper cells, Th1 cells and Th2 cells. Th1 cells contribute to cell-mediated adaptive immunity (targeting intracellular pathogens) and type IV (delayed-type) hypersensitivity reactions. On the other hand, **Th2 cells** play a prominent role in allergic response and **type I hypersensitivity reactions**.

One hypothesis for the **pathogenesis of asthma** is an excess of Th2 cell activity relative to Th1 cell activity, resulting in excessive IgE production, an abnormal propensity for type I hypersensitivity reactions, and associated chronic eosinophilic bronchitis. In the asthma **sensitization phase**, inhaled antigens stimulate Th2 cells to secrete IL-4 and other lymphokines to stimulate B-cell antibody production as part of humoral adaptive

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Repeat exposure to inhaled antigens leads to mast cell degranulation of inflammatory substances (eg, histamine, leukotrienes) and further activation of eosinophils with release of tissue-damaging substances (eg, major basic protein).

(Choice A) IL-1 is predominantly involved in the Th1 response and stimulates fever and acute inflammation. It also induces lymphokine secretion to recruit other leukocytes, including lymphocytes.

(Choice B) IL-3 is secreted by both Th1 and Th2 cells and promotes the growth and differentiation of bone marrow stem cells.

(Choice D) IL-5 is secreted by activated Th2 cells and stimulates the growth and differentiation of eosinophils. However, IL-5 promotes the class switching of B-cell immunoglobulin synthesis to IgA rather than to IgE and is a less important therapeutic target for asthma than IL-4.

(Choice E) Interferon-gamma secreted by Th1 cells activates macrophages and, along with IL-2, stimulates CD8+ cytotoxic T cells. It also inhibits the differentiation of Th2 cells.

(Choice F) Transforming growth factor-beta (TGF-β) is involved in tissue regeneration and repair. It can be produced by T lymphocytes, platelets, macrophages, endothelial cells, smooth muscle cells, fibroblasts, and keratinocytes.

Educational objective:
An excess of Th2 cell activity relative to Th1 cell activity may underlie the pathogenesis of asthma. In the asthma sensitization phase, inhaled antigens stimulate Th2 cells to secrete IL-4 and IL-13, which together promote B-lymphocyte class switching for IgE synthesis, leading to mast cell priming. Th2 cells also secrete IL-5, which activates eosinophils.

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Immunology	Pulmonary & Critical Care	Asthma
Subject	System	Topic

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A 56-year-old man hospitalized in the intensive care unit is being evaluated for fever. He was admitted 8 days ago with respiratory failure and has had a complicated hospital course, including mechanical ventilation, central venous line placement, and broad-spectrum antibiotic therapy. The patient has a history of HIV and a hematologic malignancy. His last chemotherapy session was 2 weeks ago. Chest x-ray does not reveal a new infiltrate, and urine cultures are negative for infection. Blood cultures grow pseudohyphae-producing yeast species with an ability to form germ tubes. Which of the following most likely directly contributed to the development of fungemia in this patient?

A. Complement deficiency

B. Hypogammaglobulinemia

C. Low eosinophil count

D. Low neutrophil count

E. Low T-lymphocyte count

Submit

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- A. Complement deficiency (2%)
- B. Hypogammaglobulinemia (4%)
- C. Low eosinophil count (4%)
- ✓ D. Low neutrophil count (22%)
- E. Low T-lymphocyte count (65%)

Omitted
Correct answer
D

22%
Answered correctly

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Explanation

This patient with HIV likely has **candidemia**, a disseminated form of *Candida* infection. *Candida* exists as a single-celled budding yeast with pseudohyphae (*C albicans* also exhibits "germ tubes," hyphal structures formed when the organism is grown in a specific nutritionally rich serum). *Candida* is a component of normal human skin and mucous membrane flora and is an opportunistic pathogen (does not cause disseminated infection in healthy people). Host defense is provided by 2 immune system components with distinct functions:

Explanation

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1. **T lymphocytes** (in particular T_H cells) are important for prevention of **superficial** *Candida* infection (eg, oral/esophageal candidiasis, cutaneous candidiasis, *Candida* vulvovaginitis). Conditions such as HIV (low T-cell count) increase the risk of superficial candidiasis.
2. **Neutrophils** prevent the **hematogenous** spread of *Candida*. **Disseminated** candidiasis (eg, candidemia, endocarditis) is more likely in patients who are neutropenic or otherwise immunocompromised (eg, cancer with chemotherapy) and in those with inherited impairments of phagocytosis.

The interplay of these 2 components can be seen in patients with HIV. These patients frequently have superficial *Candida* infections given their low T-cell counts, but they do not typically suffer from disseminated candidiasis as a result of HIV itself. If they also have neutropenia, there is a risk for both localized and disseminated candidiasis.

(Choice A) Deficiency of complement components C1, C2, and C4 leads to increased susceptibility to infections and systemic lupus erythematosus-like disease. Low levels of C5, C6, C7, C8, and C9 predispose individuals to infections with *Neisseria gonorrhea* and *N meningitidis*.

(Choice B) Hypogammaglobulinemia predisposes patients to bacterial infections. Neither superficial nor systemic candidiasis is associated with low gammaglobulin levels.

(Choice C) Low eosinophil counts are not associated with fungal infections.

(Choice E) This patient's HIV increases the risk of superficial *Candida* infections. However, fungemia is a disseminated rather than a localized (superficial) infection.

Educational objective:
Local defense against *Candida* is performed by T cells, whereas systemic infection is prevented by neutrophils. For this reason, localized

2. **Neutrophils** prevent the **hematogenous** spread of *Candida*. **Disseminated** candidiasis (eg, candidemia, endocarditis) is more likely in patients who are neutropenic or otherwise immunocompromised (eg, cancer with chemotherapy) and in those with inherited impairments of phagocytosis.

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Educational objective:
Local defense against *Candida* is performed by T cells, whereas systemic infection is prevented by neutrophils. For this reason, localized candidiasis is common in patients who have HIV, but neutropenic individuals are more likely to have the systemic form of the disease.

References

- Innate versus adaptive immunity in Candida albicans infection.

Immunology	Infectious Diseases	Febrile neutropenia
Subject	System	Topic

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A 37-year-old woman is evaluated for progressive shortness of breath and dry cough. The patient has seasonal allergies and takes no medications. There is no significant family history. On physical examination, the lungs are clear to auscultation. Chest imaging studies reveal pulmonary infiltrates and hilar adenopathy. The patient undergoes lung biopsy; the findings are shown below.

Which of the following sets of cells and cell products most likely directly contributed to this pathologic finding?

- A. Th1, IL-2, interferon-γ
- B. Th1, IL-5, IL-10
- C. Th2, IL-3, interferon-γ
- D. Th2, IL-4, IL-5
- E. Th2, IL-5, tumor necrosis factor-alpha

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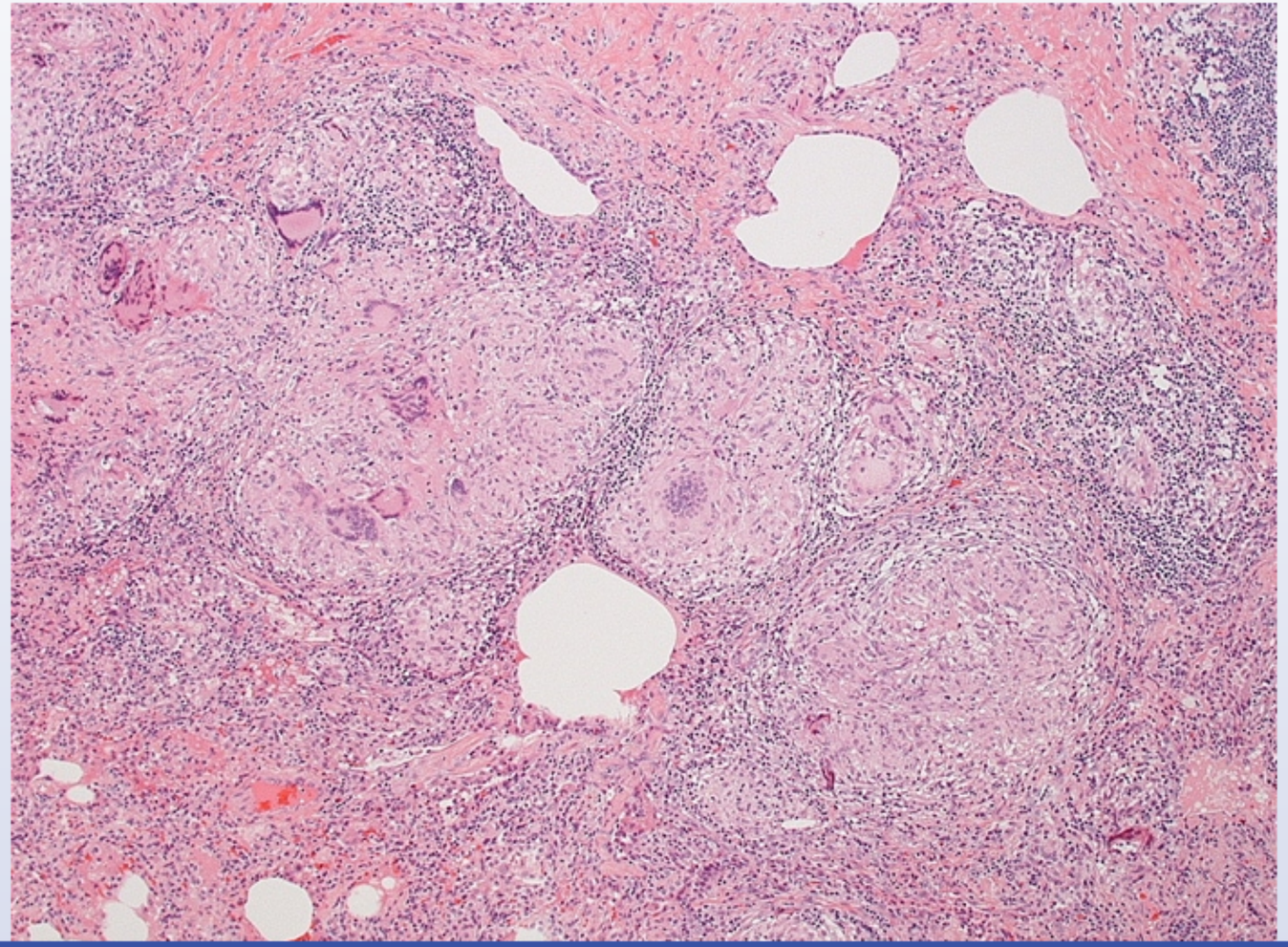
A 37-year-old woman is evaluated for progressive shortness of breath and dry cough. The patient has seasonal allergies and takes no medications. There is no significant family history. On physical examination, the lungs are clear to auscultation. Chest imaging studies reveal pulmonary infiltrates and hilar adenopathy. The patient undergoes lung biopsy; the findings are shown below.



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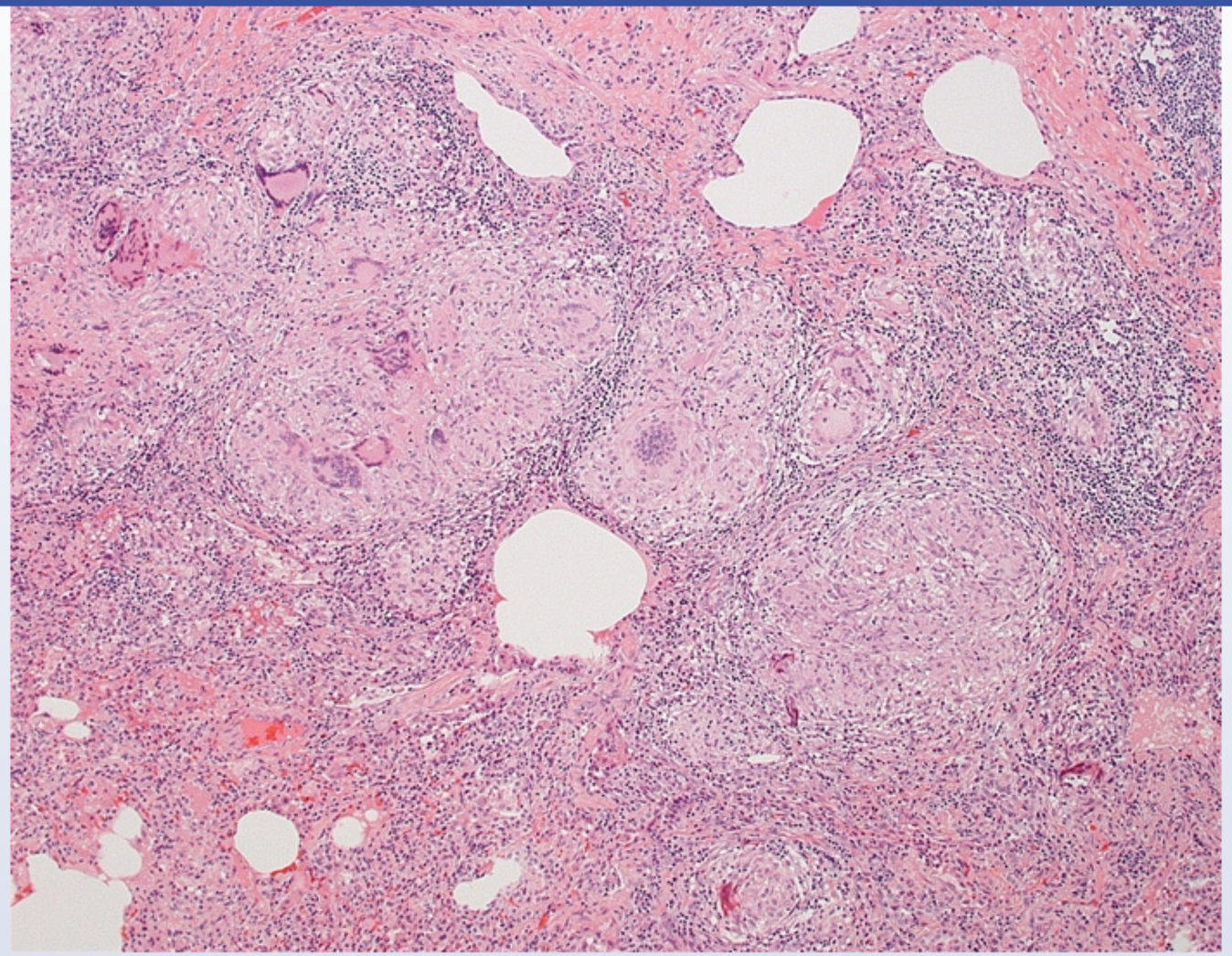

Which of the following sets of cells and cell products most likely directly contributed to this pathologic finding?

A. Th1, IL-2, interferon-γ

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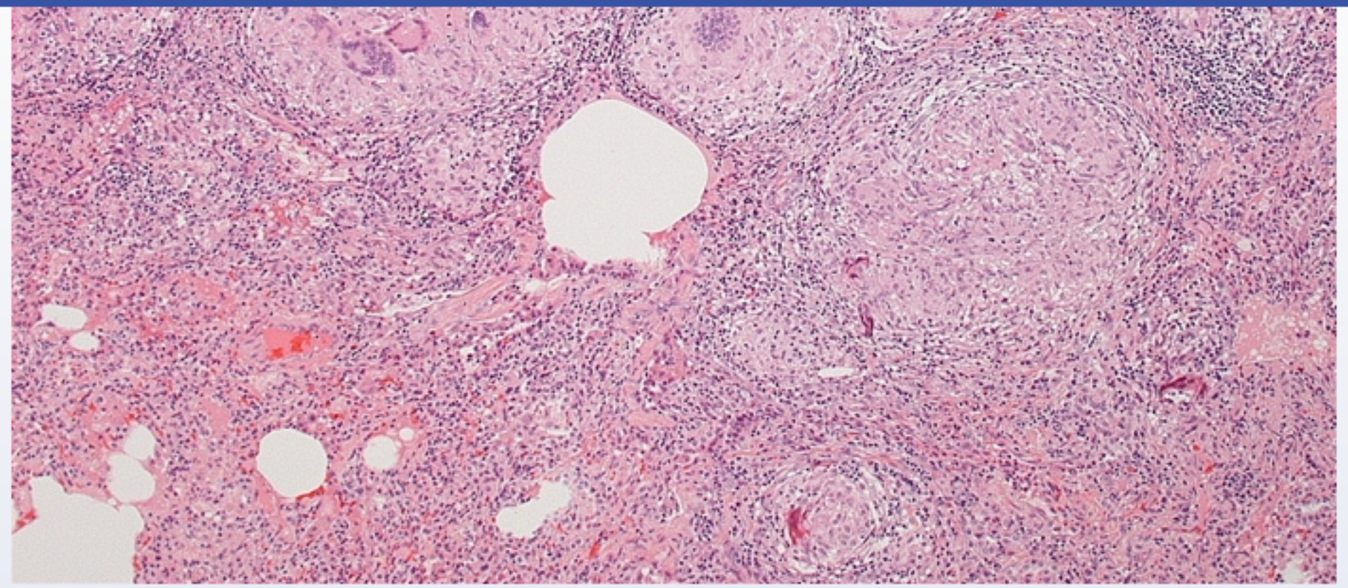

Which of the following sets of cells and cell products most likely directly contributed to this pathologic finding?

A. Th1, IL-2, interferon-γ

B. Th1, IL-5, IL-10

C. Th2, IL-3, interferon-γ

D. Th2, IL-4, IL-5

E. Th2, IL-5, tumor necrosis factor-alpha

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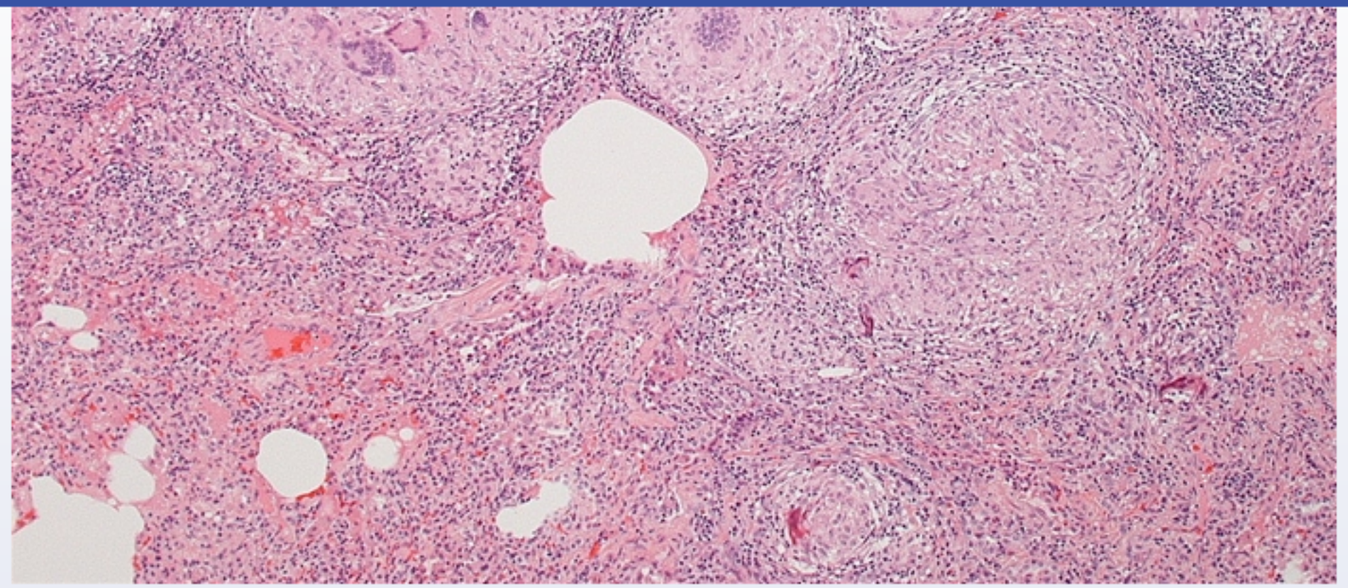

Which of the following sets of cells and cell products most likely directly contributed to this pathologic finding?

- A. Th1, IL-2, interferon-γ (68%)
- B. Th1, IL-5, IL-10 (1%)
- C. Th2, IL-3, interferon-γ (6%)
- D. Th2, IL-4, IL-5 (12%)
- E. Th2, IL-5, tumor necrosis factor-alpha (10%)

Omitted
Correct answer

68%
Answered correctly

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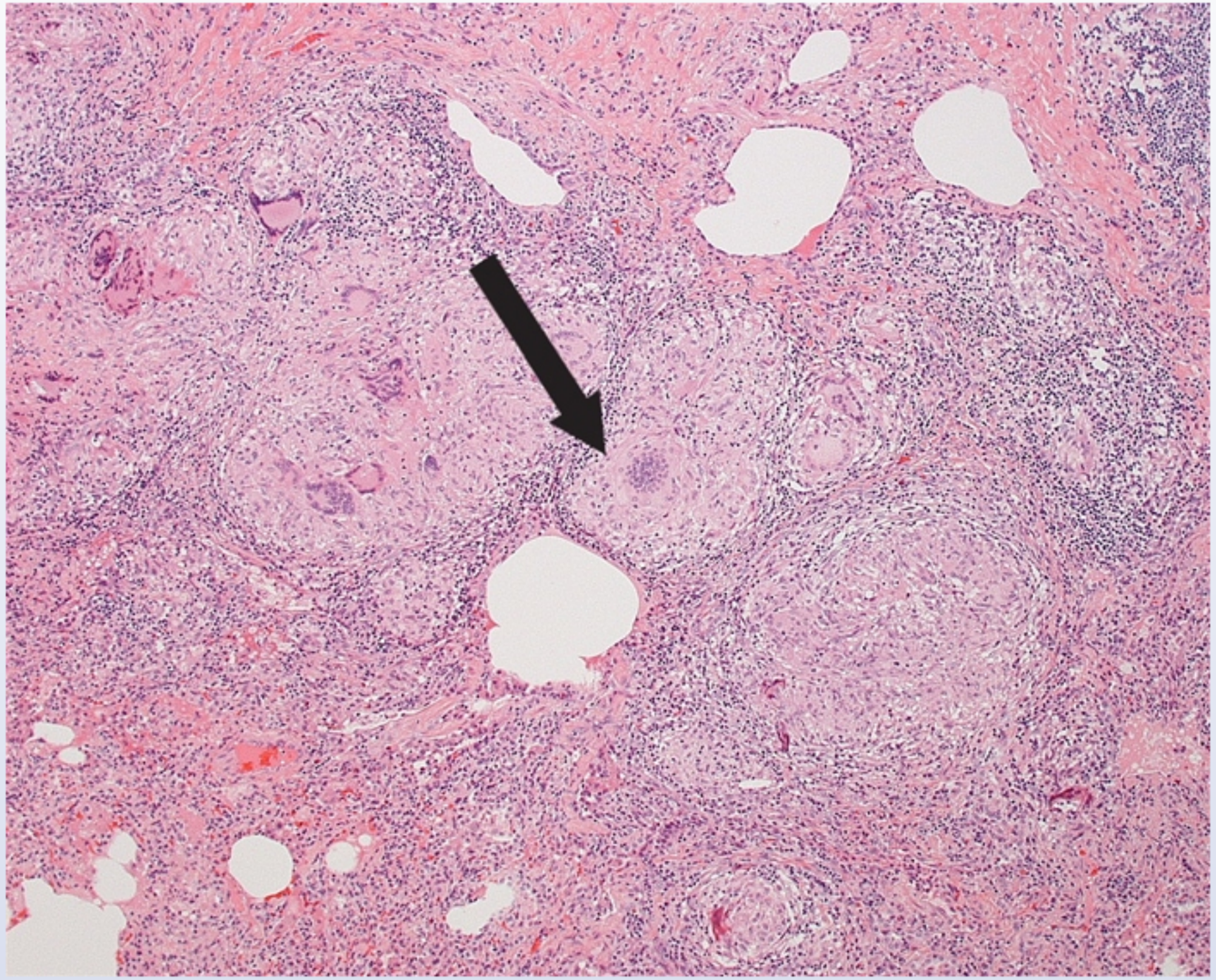
Explanation



This patient with dyspnea and dry cough has pulmonary infiltrates and hilar adenopathy; this presentation suggests pulmonary **sarcoidosis**. The biopsy specimen with multiple, **noncaseating granulomas**—characterized by a central collection of tightly clustered epithelioid macrophages with abundant pink cytoplasm surrounded by a rim of mononuclear cells—confirms the diagnosis. Multinucleated giant cells, formed by macrophage fusion, are discernable at higher magnification.

Sarcoidosis is thought to result from a dysregulated cell-mediated immune response to an unidentified antigen, which causes the formation of granulomas. **Cell-mediated immunity** is driven by the **Th1 subtype of CD4⁺ helper T cells**. Activated antigen-presenting cells produce IL-12, which stimulates the differentiation of Th1 cells. Th1 cells secrete **IL-2** and **interferon-γ** (IFN-γ). IL-2 stimulates the autocrine proliferation of Th1 cells and further Th1 recruitment. IFN-γ activates macrophages, promoting granuloma formation. Activated macrophages and T cells also produce **tumor necrosis factor-alpha**, further assisting in leukocyte recruitment and granuloma maintenance.

(Choice B) Th1 cells are central to cell-mediated immunity. However, IL-5 is a product of Th2 cells. Moreover, IL-10 is a cytokine involved in the downregulation of immune responses.

(Choices C, D, and E) Th2 cells are involved in humoral immunity and defense against extracellular parasites. Asthma, a Th2-driven disease, causes dyspnea and cough but is not associated with granuloma formation. Cytokines involved with asthma include IL-4 and IL-5, which are secreted by Th2 cells. IL-4 promotes B-cell class switching to form IgE antibodies, and IL-5 promotes eosinophil production and activation. IL-3 is also involved in asthma (as it promotes survival of mast cells) but mainly supports the growth and differentiation of bone marrow stem cells.

Educational objective:
Sarcoidosis is characterized by noncaseating granulomas due to dysregulated cell-mediated immunity. Activated antigen-presenting cells produce IL-12, which stimulates the differentiation of Th1-type CD4⁺ cells. Th1 cells produce IL-2 and interferon-γ, which stimulate Th1 cell proliferation and macrophage activation, respectively.

Immunology	Pulmonary & Critical Care	Sarcoidosis
Subject	System	Topic

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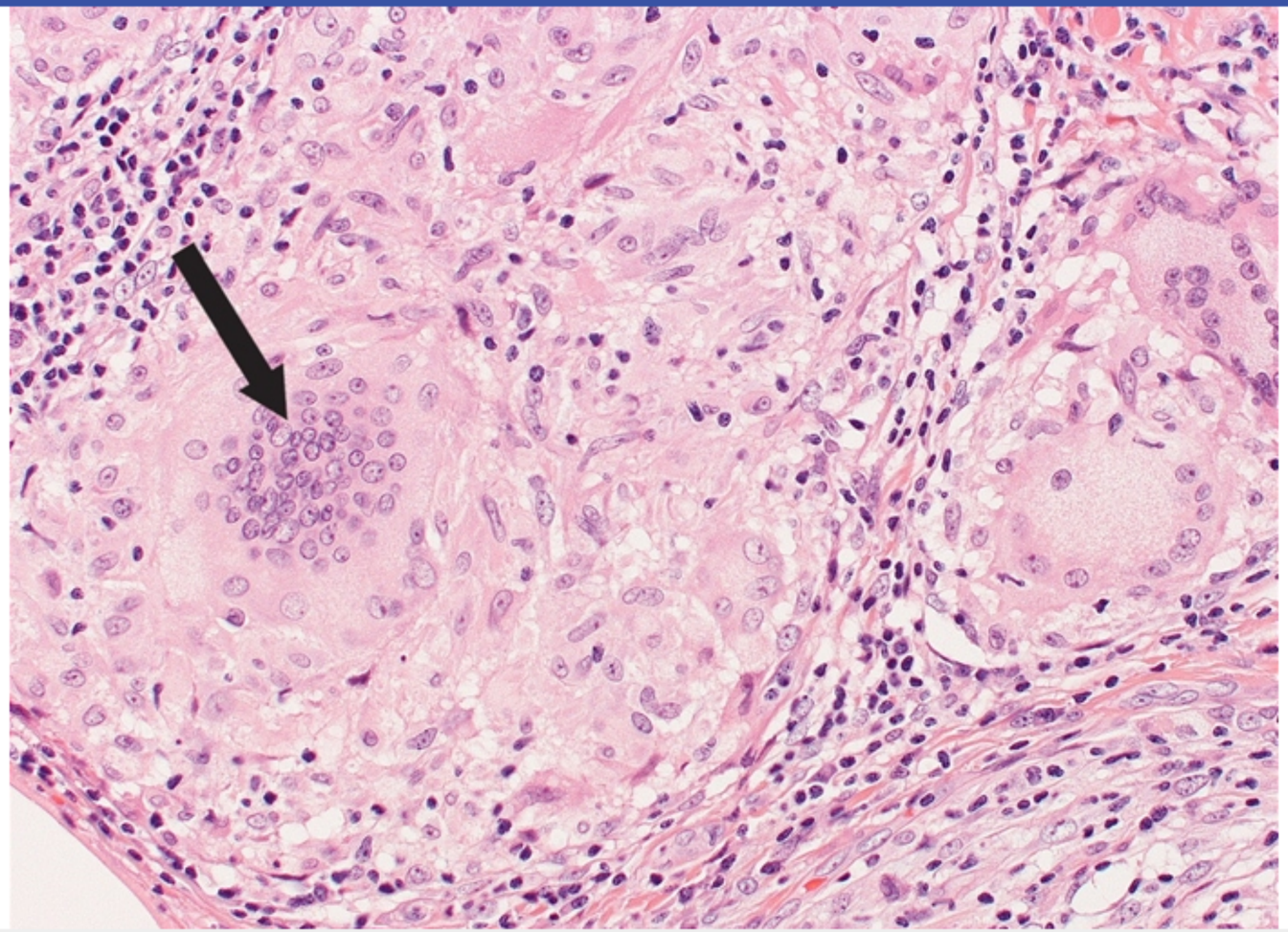

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A 34-year-old man comes to the office due to disabling fatigue. The patient was diagnosed with paroxysmal nocturnal hemoglobinuria 3 years prior and has required numerous blood transfusions due to anemia. Treatment will be initiated with a monoclonal antibody to the complement component C5. This patient requires immunization and prophylactic pharmacotherapy to prevent infection with which of the following organisms?

A. *Escherichia coli*

B. Herpes zoster virus

C. *Mycobacterium tuberculosis*

D. *Neisseria meningitidis*

E. *Staphylococcus aureus*

Submit

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A. *Escherichia coli* (1%)

B. Herpes zoster virus (0%)

C. *Mycobacterium tuberculosis* (3%)

✓ D. *Neisseria meningitidis* (92%)

E. *Staphylococcus aureus* (2%)

Omitted
Correct answer
D

92%
Answered correctly

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03/13/2020
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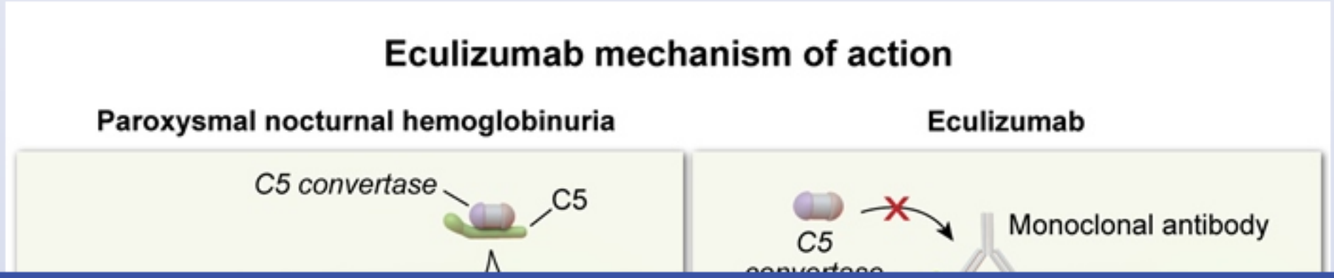
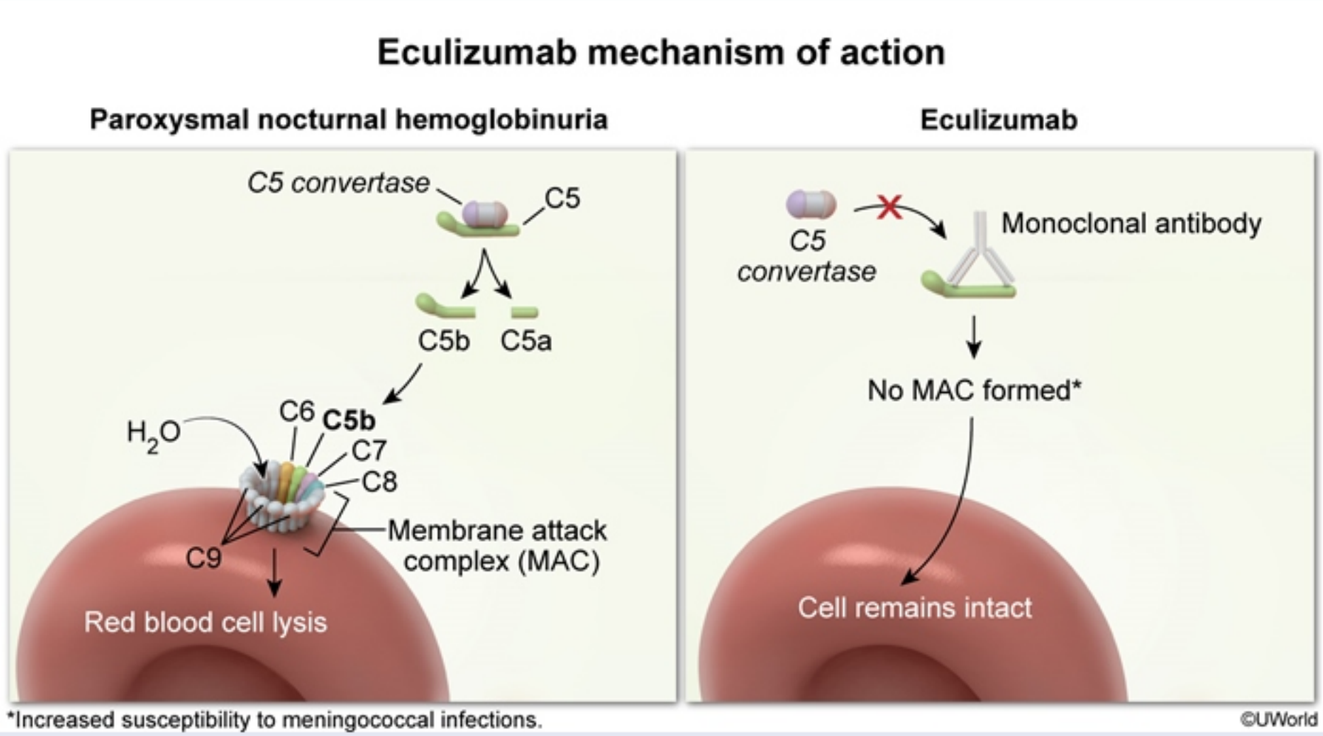
Explanation





This patient has **paroxysmal nocturnal hemoglobinuria** (PNH), a condition resulting from decreased expression of complement-inactivating proteins (eg, CD55, CD59) on the surface of red blood cells. This leads to increased formation of the membrane attack complex (MAC) (eg, complement components C5b-C9), resulting in anemia due to **complement-mediated hemolysis**. Patients with debilitating PNH symptoms (eg, fatigue, thrombosis, transfusion requirement) are often **treated with a monoclonal antibody** (eg, eculizumab) to a terminal complement component (ie, C5), which **inhibits the formation of MAC** and decreases the severity of PNH symptoms.

However, inhibition of terminal complement activity and MAC formation also results in **loss of the rapid complement-mediated killing** of Gram-negative bacteria, especially ***Neisseria meningitidis***, which can proliferate and disseminate quickly to cause catastrophic systemic disease. Therefore, patients receiving anti-complement therapy should be immunized against *N meningitidis* and be given appropriate antibiotic prophylaxis

*Increased susceptibility to meningococcal infections.

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(Choices A and E) Most strains of *Escherichia coli* and *Staphylococcus aureus* produce factors that evade complement or inhibit complement activation and do not replicate as rapidly as *N meningitidis*. Therefore, host defense to these pathogens depends primarily on other components of the immune system (eg, neutrophil function, humoral immunity) and would not be significantly affected by the use of a terminal complement inhibitor.

(Choices B and C) Host defense to herpes zoster virus and *Mycobacterium tuberculosis* depends more on T cell function than complement activation and MAC formation.

Educational objective:
Paroxysmal nocturnal hemoglobinuria may be treated with a monoclonal antibody to the complement component C5 (ie, terminal complement inhibitor), increasing the risk of disseminated *Neisseria meningitidis* infection. Therefore, these patients should receive immunization and antibiotic prophylaxis against *N meningitidis*.

References

- Eculizumab: a review of its use in paroxysmal nocturnal haemoglobinuria.

Immunology Infectious Diseases Meningococci

A 5-year-old boy is brought to the ER with breathing difficulty, dysphagia, drooling and fever. His temperature is 39.4C (103.0 F). White blood cell count is 23,000/cmm with many band forms. Laryngoscopy in the operating room shows a swollen and cherry-red epiglottis. This patient most likely:

- A. Traveled recently
- B. Missed vaccination
- C. Was stung by a bee
- D. Has penicillin allergy
- E. Has characteristic family history

Submit

A 5-year-old boy is brought to the ER with breathing difficulty, dysphagia, drooling and fever. His temperature is 39.4C (103.0 F). White blood cell count is 23,000/cmm with many band forms. Laryngoscopy in the operating room shows a swollen and cherry-red epiglottis. This patient most likely:

- A. Traveled recently (5%)
- ✓ B. Missed vaccination (86%)
- C. Was stung by a bee (4%)
- D. Has penicillin allergy (2%)
- E. Has characteristic family history (1%)

Omitted
Correct answer
B

86%
Answered correctly

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Explanation

Acute epiglottitis is a rapidly progressive infection of the epiglottis leading to severe inflammation and edema of the epiglottis and larynx and potentially acute obstruction of the airway especially during laryngoscopy. Small children typically present with fever and dysphagia, while older children and adults complain of sore throat. Inspiratory stridor and anxiousness due to compromised diameter of the larynx occur frequently, and patients may present with drooling. Diagnosis is confirmed by the presence of an edematous epiglottis that classically appears cherry red though inspection of the epiglottis should not be done unless the team is prepared to provide a surgical airway by tracheostomy. The most likely pathogen in children is *H. influenzae*, but the introduction of the *H. influenzae* type b (Hib) vaccine has led to a dramatic decrease in the incidence of

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The *Haemophilus influenzae* b vaccine is now a part of the routine vaccination schedule and is administered in the first few months of life. Immunity during the first couple months of life prior to this vaccination is acquired by transient maternal transplacental IgG antibodies. If a child were to miss a vaccination or not be vaccinated at all, then the child would be at an increased risk of *H. influenzae* type b infection, though Hib epiglottitis has been shown to occur in fully immunized children as well.

(Choice A) Recent travel can alert the physician to suspect diseases that are endemic to the area that the patient traveled. Epiglottitis is not associated with travel. Malaria is associated with travel in Africa, HIV is rampant in Africa and Haiti, *Coccidioides immitis* is common in the southwest United States, Blastomycosis in the Mississippi river valley and Histoplasmosis common in the Ohio River valley, but this list is by no means comprehensive of all diseases associated with geography.

(Choice C) Bee stings are not associated with bacterial infections of any kind unless the wound left by a sting becomes somehow super infected. Bee stings can induce clinical disease ranging from local allergic reactions around the site of the sting to anaphylaxis and death. Bee venom contains hyaluronidase, phospholipase, and other proteins which initiate an IgE-mediated response.

(Choice D) Penicillin allergy is not associated with epiglottitis. Adverse reactions to penicillin can range from rash and hives to angioedema, bronchospasm, and anaphylaxis.

(Choice E) Family history is not a factor in epiglottitis except for cases of heritable immune system defects that predispose to recurrent bacterial infections, but these disorders would not predispose purely to epiglottitis.

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Educational Objective:
Rapidly progressing fever, severe sore throat, drooling and progressive airway obstruction potentially accompanied by stridor are the presenting symptoms of acute epiglottitis. This illness is most commonly caused by *H. influenzae* type b, but the Hib vaccine has dropped the incidence of this disease considerably. H. influenzae type b can still cause disease in unimmunized or improperly immunized patients as well as fully immunized patients in some cases.

Immunology	Pulmonary & Critical Care	Epiglottitis
Subject	System	Topic

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A 44-year-old man with diabetic nephropathy undergoes a renal transplant. One week later, he develops low-grade fever, body aches, and decreased urine output. Temperature is 37.2 C (99 F), blood pressure is 124/76 mm Hg, and pulse is 88/min. Physical examination shows mild tenderness over the graft on palpation. Serum creatinine is 2.2 mg/dL, an increase from 1.2 mg/dL two days ago. Arterial and venous Doppler studies reveal adequate graft perfusion. Graft biopsy demonstrates dense interstitial infiltration by mononuclear cells. Which of the following is the most likely cause of this patient's current condition?

A. Graft B-cell sensitization against host MHC antigens

B. Graft T-cell sensitization against host MHC antigens

C. Host B-cell sensitization against graft MHC antigens

D. Host T-cell sensitization against graft MHC antigens

E. Preformed antibodies against graft ABO antigens

Submit

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- A. Graft B-cell sensitization against host MHC antigens (2%)
- B. Graft T-cell sensitization against host MHC antigens (15%)
- C. Host B-cell sensitization against graft MHC antigens (12%)
- ✓ D. Host T-cell sensitization against graft MHC antigens (67%)
- E. Preformed antibodies against graft ABO antigens (2%)

Omitted
Correct answer
D

67%
Answered correctly

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Explanation

Transplant rejection reactions			
Type of rejection	Onset time	Etiology	Morphology

Transplant rejection reactions			
Type of rejection	**Onset time**	**Etiology**	**Morphology**
Hyperacute	Minutes to hours	• Preformed recipient antibodies against graft antigens	• Gross mottling & cyanosis • Arterial fibrinoid necrosis & capillary thrombotic occlusion
Acute	Usually <6 months	• Exposure to donor antigens induces activation of naive immune cells • Predominantly **cell-mediated**	• **Cellular:** lymphocytic interstitial infiltrate & endotheliitis • Humoral: C4d deposition, neutrophilic infiltrate, necrotizing vasculitis
Chronic	Months to years	• Chronic low-grade immune response refractory to immunosuppression • Predominantly **humoral**	• Vascular wall thickening & luminal narrowing • Interstitial fibrosis & parenchymal atrophy

This patient with **impaired renal function** within the first few weeks following renal transplant likely has **acute rejection**. This process is mostly **cell-mediated** and results from **sensitization of recipient T cells** to donor graft MHC antigens (human leukocyte antigens). Humoral (antibody-mediated) immunity may also be involved in acute rejection, but it typically plays a smaller role.

Acute rejection usually occurs within the **first 6 months** following transplantation. Patients often have an asymptomatic rise in serum creatinine, but they may also have low-grade fever, malaise, joint pains, and graft tenderness. Histology reveals a **dense lymphocytic infiltrate** sometimes accompanied by vascular inflammation. Acute rejection is typically reversible and usually treated with high-dose glucocorticoids. Chronic immunosuppression with a calcineurin inhibitor–based regimen (eg, tacrolimus plus mycophenolate and low-dose prednisone) helps prevent acute rejection episodes.

(Choices A and B) Graft versus host disease (GVHD) primarily involves activation of donor T cells within grafted tissue against recipient (host) antigens. B cells are also involved to a lesser extent. GVHD typically occurs only when the recipient lacks a competent immune response (eg, in

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(Choices A and B) Graft versus host disease (GVHD) primarily involves activation of donor T cells within grafted tissue against recipient (host) antigens. B cells are also involved to a lesser extent. GVHD typically occurs only when the recipient lacks a competent immune response (eg, in the setting of bone marrow transplant).

(Choice C) Host B-cell sensitization against donor antigens results in a humoral antibody response and is sometimes involved in acute rejection. Histology is expected to show deposition of complement (eg, C4d), neutrophilic infiltrate, and necrotizing vasculitis; this patient's mononuclear (lymphocytic) infiltrate is consistent with a cell-mediated T-cell response. Although it can occur acutely, the humoral response tends to be more involved in chronic rejection, which occurs months to years following transplant.

(Choice E) Preformed antibodies against graft ABO or other antigens can lead to hyperacute graft rejection. Because the antibodies are already present in the recipient circulation, there is rapid response against the donor graft, leading to arterial fibrinoid necrosis and vascular thrombosis with graft mottling and cyanosis. Thorough crossmatching prior to transplant makes hyperacute rejection a rare occurrence.

Educational objective:
Organ rejection can be hyperacute, acute, or chronic. Acute rejection most often occurs within weeks or up to 6 months after transplant and is predominantly cell-mediated, involving sensitization of host T lymphocytes against donor MHC antigens. There is typically graft dysfunction with histology showing a dense, mononuclear (ie, lymphocytic) infiltrate.

Immunology	Renal, Urinary Systems & Electrolytes	Transplant rejection
Subject	System	Topic

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A 34-year-old woman comes to the office for tuberculosis evaluation. The patient was advised to have tuberculosis testing after her father, who came to visit from Haiti a week ago and had been living with her, was found to have active pulmonary tuberculosis. She has no history of tuberculosis or any other chronic medical conditions and takes no medications. Tuberculin skin testing is performed and results 48 hours later are negative. Eight weeks later, the patient returns for follow-up and says she feels healthy and has had no fever, cough, shortness of breath, or weight loss. Physical examination shows no abnormalities. Repeat tuberculin skin testing reveals significant skin induration around the injection site at 48 hours. Chest radiograph reveals no parenchymal opacities, pleural effusion, or enlarged lymph nodes. Which of the following immune effector cells are most important for control of the pathogen responsible for this patient's skin findings?

- A. B lymphocytes and macrophages
- B. CD4 T lymphocytes and macrophages
- C. CD4 T lymphocytes and neutrophils
- D. CD8 T lymphocytes and B lymphocytes
- E. CD8 T lymphocytes and NK cells

Submit

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- A. B lymphocytes and macrophages (2%)
- ✓ B. CD4 T lymphocytes and macrophages (83%)
- C. CD4 T lymphocytes and neutrophils (3%)
- D. CD8 T lymphocytes and B lymphocytes (4%)
- E. CD8 T lymphocytes and NK cells (6%)

Omitted
Correct answer
B

83%
Answered correctly

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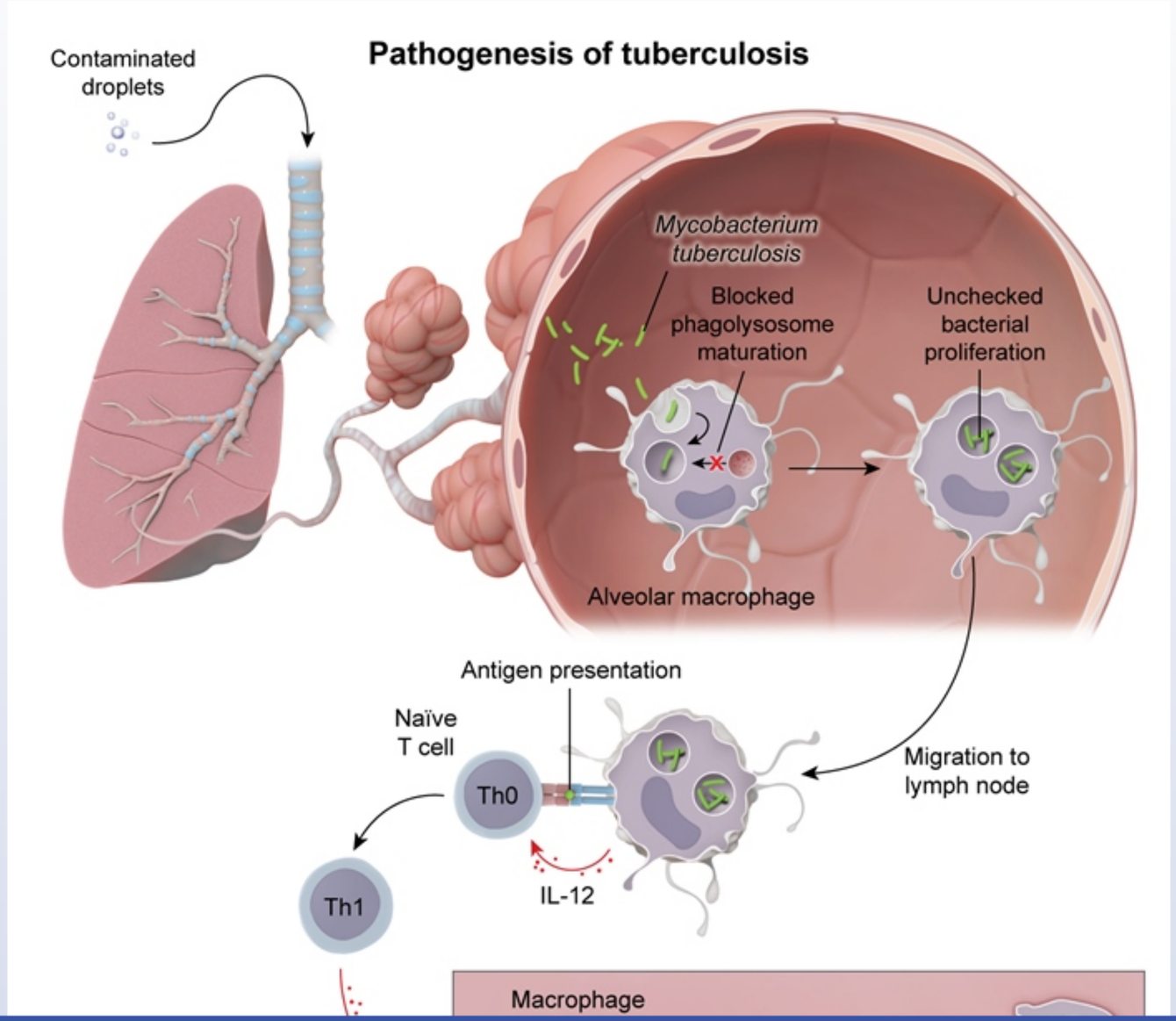
Explanation


Pathogenesis of tuberculosis
Contaminated droplets
Mycobacterium tuberculosis
Blocked phagolysosome maturation
Unchecked bacterial proliferation
Alveolar macrophage
Antigen presentation
Naïve T cell
Th0
Th1
IL-12
Migration to lymph node
Macrophage

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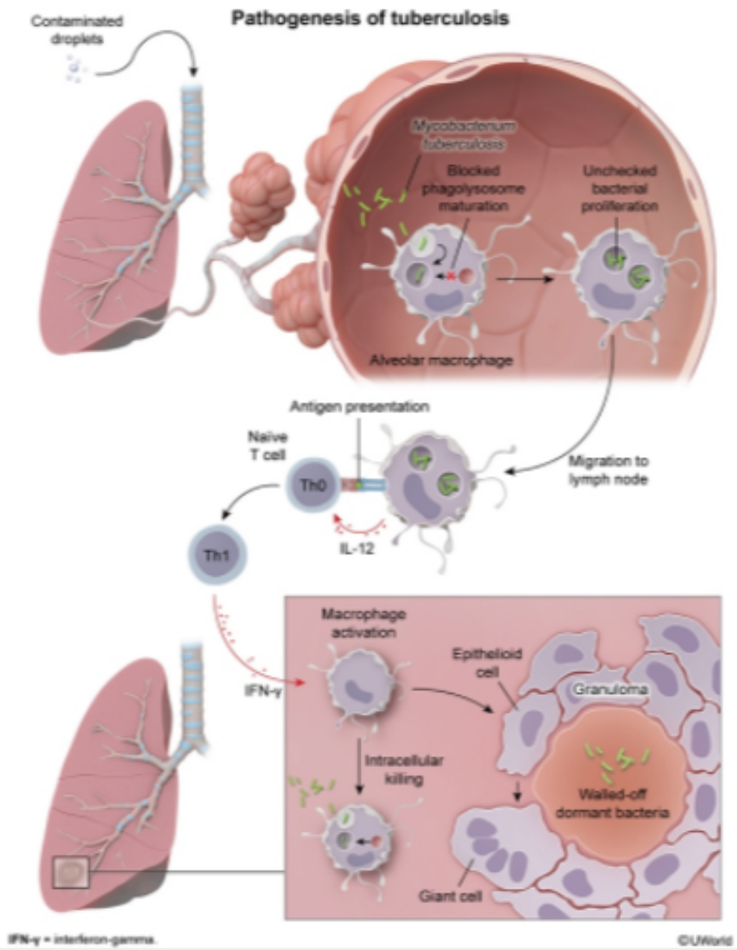

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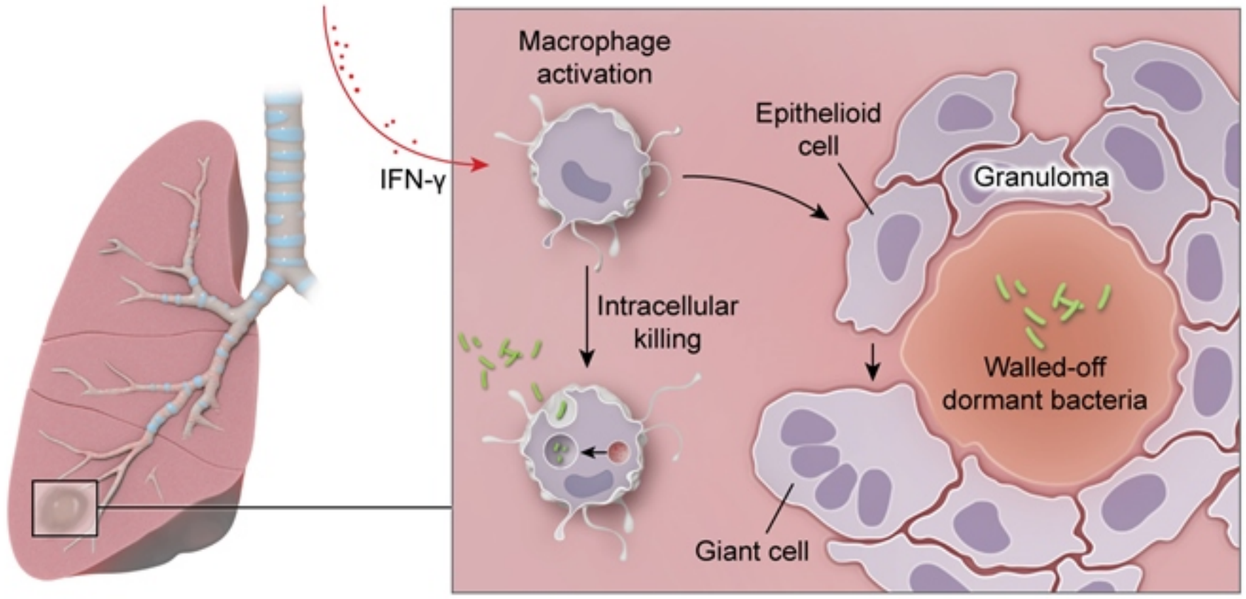
Macrophage



IFN-γ = interferon-gamma.

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Mycobacterium tuberculosis is transmitted by aerosolized droplets from a patient with active pulmonary tuberculosis. Initially, the pathogen replicates in an unchecked fashion due to virulence factors (eg, cord factor) that allow the bacteria to escape destruction within the phagolysosomes of alveolar macrophages. After a few weeks, antigen-presenting cells in the draining lymphatic system display mycobacterial antigens on major compatibility complex class II molecules and release **interleukin-12**, which differentiates **naïve CD4 cells** into T-helper subtype-1 (**Th1**) cells.

Th1 cells migrate to the sites of infection and secrete **interferon-gamma**, resulting in the **activation of macrophages**. Activated macrophages are able to form fully mature phagolysosomes to destroy intracellular mycobacteria. They also differentiate into cells (eg, epithelioid, Langhans giant cells) that surround extracellular mycobacteria and form granulomas. Granulomas have an acidic, hypoxic central environment that limits the proliferation of mycobacteria but does not usually eliminate the infection.

The tuberculin skin test (TST) is a common screening test for *M tuberculosis* exposure. It involves injection of tuberculin antigens into the skin

IFN-γ = interferon-gamma.

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Mycobacterium tuberculosis is transmitted by aerosolized droplets from a patient with active pulmonary tuberculosis. Initially, the pathogen replicates in an unchecked fashion due to virulence factors (eg, cord factor) that allow the bacteria to escape destruction within the phagolysosomes of alveolar macrophages. After a few weeks, antigen-presenting cells in the draining lymphatic system display mycobacterial antigens on major compatibility complex class II molecules and release **interleukin-12**, which differentiates **naïve CD4 cells** into T-helper subtype-1 (**Th1**) cells.

Th1 cells migrate to the sites of infection and secrete **interferon-gamma**, resulting in the **activation of macrophages**. Activated macrophages are able to form fully mature phagolysosomes to destroy intracellular mycobacteria. They also differentiate into cells (eg, epithelioid, Langhans giant cells) that surround extracellular mycobacteria and form granulomas. Granulomas have an acidic, hypoxic central environment that limits the proliferation of mycobacteria but does not usually eliminate the infection.

The tuberculin skin test (TST) is a common screening test for *M tuberculosis* exposure. It involves injection of tuberculin antigens into the skin, which provokes a T-cell-mediated, delayed-type hypersensitivity reaction in those who have been previously exposed (induration at 48-72 hours). Because the cell-mediated response to *M tuberculosis* takes several weeks to form, recently exposed patients often have negative initial TST testing. Conversion usually occurs within 8 weeks.

Most patients with primary tuberculosis have no symptoms and no chest x-ray findings; however, after several months, a Ranke complex (calcified lower lobe nodule and ipsilateral hilar lymph node) can often be seen on x-ray.

(Choice A) Facultative, intracellular organisms such as *M tuberculosis* are protected from antibodies and complement when within cells. As a result, elimination of these pathogens does not primarily rely on the humoral immune system (eg, B lymphocytes).

(Choice C) Neutrophils are the crucial immune component for initial control of most extracellular bacterial infections (eg, *Streptococcus pneumoniae*). Macrophages are the critical immune effector cell in patients with *M tuberculosis* and most other intracellular infections (in combination with T lymphocytes).

(Choice D) Intracellular organisms that replicate in the cytosol, such as viruses or certain intracellular bacteria (eg, *Listeria*), are processed by the proteasome and displayed on major histocompatibility complex (MHC) class I molecules. This leads to the activation of CD8 T lymphocytes. *M tuberculosis* primarily replicates within the phagosome (not the cytosol), leading to display of mycobacterial antigens on MHC class II molecules and the subsequent activation of CD4, rather than CD8, cells.

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(Choice E) Natural killer cells are cytotoxic lymphocytes that can recognize damaged or infected cells without MHC activation. They are important for clearing viral infections and for tumor immunosurveillance, but are not the primary effector cell in tuberculosis infection.

Educational objective:
Mycobacteria tuberculosis primarily replicates within the phagosome, leading to display of mycobacterial antigens on major histocompatibility complex class II molecules. This results in the activation of CD4 cells and subsequent control of the infection with macrophages.

References

- The tuberculous granuloma: an unsuccessful host defence mechanism providing a safety shelter for the bacteria?
- Immunology of tuberculosis.
- Th1 and Th17 cells in tuberculosis: protection, pathology, and biomarkers.

Immunology	Pulmonary & Critical Care	Tuberculosis
Subject	System	Topic

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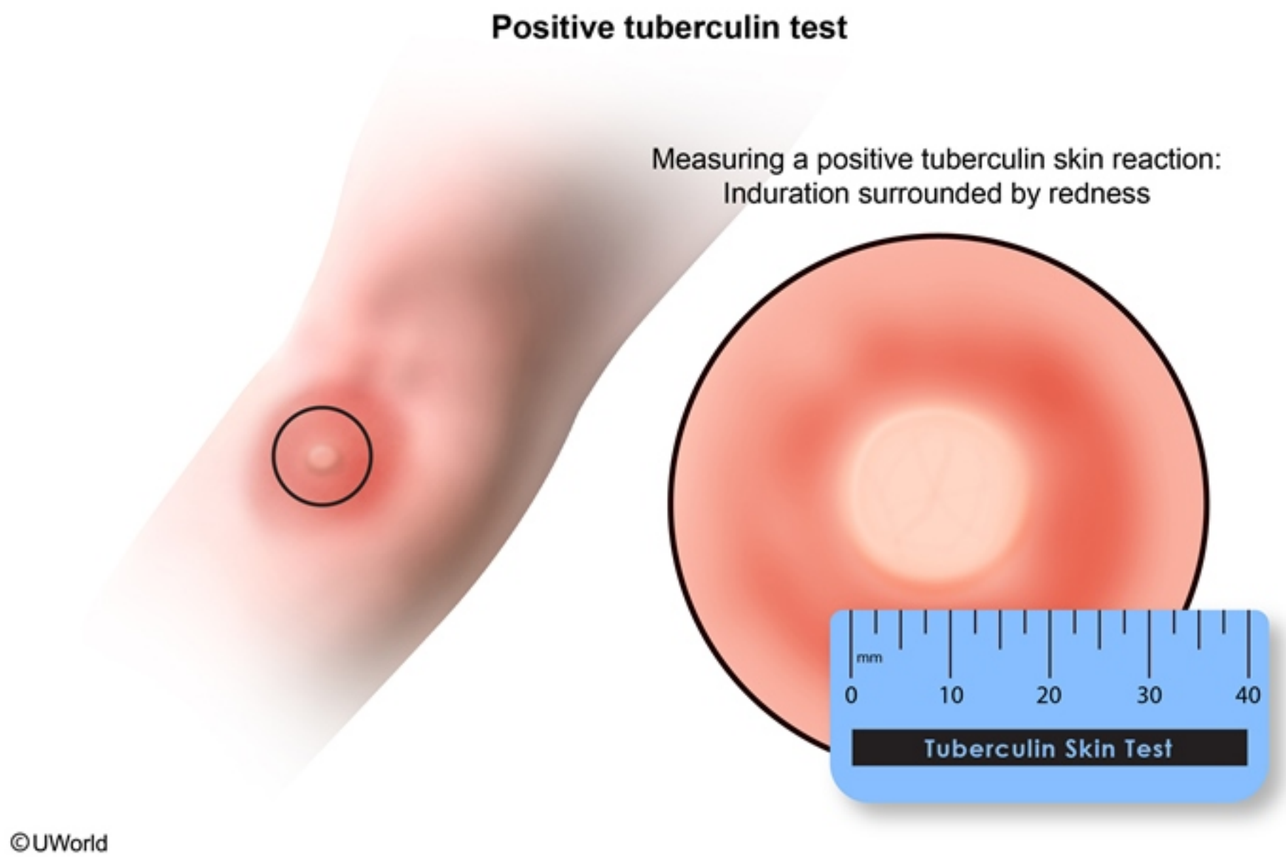
Giant cell

Exhibit Display



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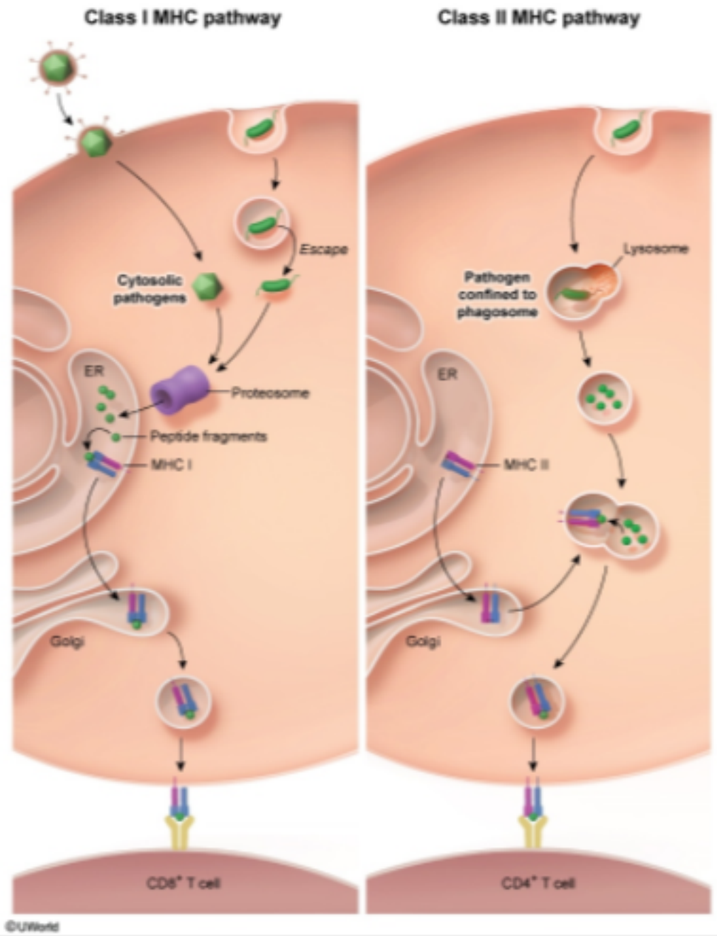

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A 45-year-old man comes to clinic for routine follow-up. He has a history of end-stage renal disease due to autosomal dominant polycystic kidney disease, and he underwent a deceased-donor kidney transplant 4 years ago. The patient has hypertension that initially resolved following the transplant but redeveloped 6 months ago. Review of his recent laboratory studies reveals a progressive increase in serum creatinine levels over the last few months. Urinalysis is within normal limits. On ultrasonography, the transplanted kidney is reduced in size. A biopsy of the graft is most likely to show which of the following?

A. Dense mononuclear interstitial infiltration

B. Glomerular crescent formation

C. Obliterative vascular fibrosis

D. Tubular hypertrophy and intratubular casts

E. Vascular fibrinoid necrosis with thrombotic occlusion

Submit

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- A. Dense mononuclear interstitial infiltration (18%)
- B. Glomerular crescent formation (4%)
- ✓ C. Obliterative vascular fibrosis (53%)
- D. Tubular hypertrophy and intratubular casts (3%)
- E. Vascular fibrinoid necrosis with thrombotic occlusion (19%)

Omitted
Correct answer
C

53%
Answered correctly

02 secs
Time Spent

03/19/2020
Last Updated

Explanation

Transplant rejection reactions			
Type of rejection	Onset time	Etiology	Morphology

Transplant rejection reactions			
Type of rejection	**Onset time**	**Etiology**	**Morphology**
Hyperacute	Minutes to hours	• Preformed recipient antibodies against graft antigens	• Gross mottling & cyanosis • Arterial fibrinoid necrosis & capillary thrombotic occlusion
Acute	Usually <6 months	• Exposure to donor antigens induces activation of naive immune cells • Predominantly **cell-mediated**	• **Cellular:** lymphocytic interstitial infiltrate & endotheliitis • Humoral: C4d deposition, neutrophilic infiltrate, necrotizing vasculitis
Chronic	Months to years	• Chronic low-grade immune response refractory to immunosuppression • Predominantly **humoral**	• Vascular wall thickening & luminal narrowing • Interstitial fibrosis & parenchymal atrophy

This kidney transplant recipient with **progressive decline in renal function** most likely has **chronic allograft rejection**. The process is mostly **antibody-mediated** and can occur anytime from **several months to years** posttransplantation.

Following transplant, recipient antibodies are created to graft HLA and other antigens and can initially contribute to acute rejection, which is generally reversible via an increase in immunosuppression (eg, high-dose glucocorticoids). Chronic rejection represents progression of antibody-mediated inflammation (eg, via activation of complement and recruitment of neutrophils) to the point that **irreversible** renal damage takes place; the kidney grossly decreases in size, and histopathology shows **obliterative vascular wall thickening** with **tubular atrophy** and **interstitial fibrosis**.

Due to increased sodium retention, declining renal function in chronic rejection is also commonly accompanied by new or worsening **hypertension**. Chronic rejection is the most common cause of renal graft failure following transplant.

(Choice A) A dense, interstitial, mononuclear (lymphocytic) infiltrate is characteristic of acute allograft rejection, which is most often a primarily T

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(Choice A) A dense, interstitial, mononuclear (lymphocytic) infiltrate is characteristic of acute allograft rejection, which is most often a primarily T cell–mediated process. Acute rejection typically occurs <6 months after transplant but can occur later in a patient in whom posttransplant immunosuppression has been stopped.

(Choice B) Glomerular injury in chronic rejection is predominantly ischemic, and crescent formation is not typically observed. Crescents develop mainly in anti–glomerular basement membrane antibody–mediated, antineutrophilic cytoplasmic autoantibody–associated, or immune complex–mediated glomerulonephritis.

(Choice D) Muddy brown casts can be seen with acute tubular necrosis, which usually manifests as acute (rather than gradual) kidney injury. Tubular hypertrophy may be present during the recovery phase. These findings are not typical of chronic rejection.

(Choice E) Vascular fibrinoid necrosis with capillary thrombotic occlusion occurs in hyperacute rejection, which is a rapid and profound form of antibody-mediated rejection caused by *preformed* antibodies to graft antigens. Chronic rejection is a more gradual antibody-mediated process resulting from sensitization that occurs after a transplant has taken place.

Educational objective:
Chronic renal allograft rejection manifests months to years after a transplant and presents with worsening hypertension and a gradual decline in renal function. It involves a chronic, antibody-mediated response against donor antigens and leads to obliterative vascular wall thickening, tubular atrophy, and interstitial fibrosis. The process is usually irreversible and eventually leads to graft failure.

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Immunology	Renal, Urinary Systems & Electrolytes	Transplant rejection
Subject	System	Topic

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A 7-year-old boy is brought to the clinic by his parents after developing red urine earlier in the day. The patient has asthma, allergic rhinitis, and atopic dermatitis. He was recently treated for a skin infection. Blood pressure is 140/90 mm Hg. On physical examination, there is periorbital edema as well as pitting edema on both feet. Laboratory results are as follows:

Serum chemistry

Blood urea nitrogen	14 mg/dL
Creatinine	1.4 mg/dL

Which of the following is most likely responsible for this patient's renal injury?

A. $CD8^+$ T lymphocytes
B. Histamine release
C. IgG autoantibodies
D. IgG immune complexes
E. Macrophages

Submit

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Serum chemistry

Blood urea nitrogen	14 mg/dL
Creatinine	1.4 mg/dL

Which of the following is most likely responsible for this patient's renal injury?

A. $CD8^+$ T lymphocytes (3%)
B. Histamine release (6%)
C. IgG autoantibodies (10%)
✓ D. IgG immune complexes (78%)
E. Macrophages (1%)

Omitted
Correct answer
D

78%
Answered correctly

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Time Spent

05/10/2020
Last Updated

Explanation

Hypersensitivity reactions			
	Humoral components	**Cellular components**	**Examples**
Type I (immediate)	• **IgE**	• Basophils • Mast cells	• Anaphylaxis • Allergies
Type II (cytotoxic)	• **IgG & IgM** autoantibodies • Complement activation	• NK cells • Eosinophils • Neutrophils • Macrophages	• Autoimmune hemolytic anemia • Goodpasture syndrome
Type III (immune complex)	• Deposition of **antibody-antigen complexes** • Complement activation	• Neutrophils	• Serum sickness • PSGN • Lupus nephritis
Type IV (delayed type)	• None	• **T cells** • **Macrophages**	• Contact dermatitis • Tuberculin skin test

NK = natural killer; **PSGN** = poststreptococcal glomerulonephritis.

This patient with atopic dermatitis is predisposed to secondary skin infections (eg, impetigo, cellulitis). His **antecedent skin infection**, along with nephritic syndrome, suggests **poststreptococcal glomerulonephritis** (PSGN), the most common form of acute nephritis in children.

During infection, antibodies form against antigens expressed by nephritogenic strains of **group A beta-hemolytic *Streptococcus*** (eg, *S pyogenes*). These antistreptococcal antibodies combine with streptococcal antigens to form **immune complexes** that are deposited along the glomerular basement membrane (**type III hypersensitivity**). These deposits can then be visualized as electron-dense **subepithelial** "humps" on electron microscopy and as **granular depositions** within the mesangium and glomerular capillary walls on IgG and C3 immunofluorescence.

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(Choices A and E) Cytotoxic $CD8^+$ T lymphocytes and macrophages play a prominent role in type IV (delayed-type) hypersensitivity reactions. These cells are stimulated by T helper cells, leading to localized inflammation, cellular destruction, and granuloma formation. Type IV hypersensitivity is responsible for contact dermatitis (eg, poison ivy) and positive tuberculin skin test reactions.

(Choice B) Histamine is released by mast cells and basophils during type I (immediate) hypersensitivity, which is seen in anaphylaxis and allergies, not in PSGN. Mast cells and basophils are coated by IgE molecules, which cross-link on antigen exposure, triggering the release of histamine and other mediators.

(Choice C) Autoantibodies are responsible for type II (cytotoxic) hypersensitivity reactions. This reaction is responsible for Goodpasture syndrome (antibodies directed at type IV collagen), which can cause nephritic syndrome and hemoptysis. However, it is rare in children and is not associated with recent streptococcal infection. Other type II hypersensitivity reactions include autoimmune hemolytic anemia, immune thrombocytopenic purpura, and pemphigus vulgaris.

Educational objective:
Poststreptococcal glomerulonephritis is the most common cause of nephritic syndrome (eg, hematuria, edema, hypertension) in children, typically occuring 2-4 weeks after a streptococcal infection (eg, impetigo, cellulitis, pharyngitis). It is caused by a type III (immune-complex–mediated) hypersensitivity reaction resulting from nephritogenic strains of group A beta-hemolytic *Streptococcus*.

Immunology	Renal, Urinary Systems & Electrolytes	Poststreptococcal Glomerulonephritis
Subject	System	Topic

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This patient with atopic de ... with nephritic syndrome, sugge

During infection, antibodie ... *pyogenes*). These antistre ... glomerular basement mer ... on electron microscopy and a

(Choices A and E) Cytot ... These cells are stimulated ... hypersensitivity is respons ...

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(Choice C) Autoantibodie ... syndrome (antibodies dire ... not associated with recent str ... thrombocytopenic purpura

Educational objective:
Poststreptococcal glomeru ... ally occuring 2-4 weeks after a ... hypersensitivity reaction re

Immunology — Subject
Renal, Urinary Systems & Electrolytes — System
Poststreptococcal Glomerulonephritis — Topic

Exhibit Display

Nephritic vs nephrotic syndrome

	Nephritic	Nephrotic
Onset	Abrupt	Insidious
GFR	Low	Normal or low
Serum albumin	Normal	Low
Edema	±	++
Hypertension	++	±
Casts	RBC casts	Fatty or none
Proteinuria	±	++
Hematuria	++	±
Pyuria	+	None

GFR = glomerular filtration rate; RBC = red blood cell.
+ = present; ++ = significant.

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Immunology	Renal, Urinary Systems & Electrolytes	Poststreptococcal Glomerulonephritis
Subject	System	Topic

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A 24-year-old hospital phlebotomist comes to the occupational health clinic after sustaining a needlestick injury while drawing blood from a hepatitis B–positive patient. She has no medical history and received the complete hepatitis B vaccination series prior to her hospital employment a year ago. She is closely monitored over the next 6 months with repeat hepatitis B serologies and does not develop clinical or laboratory evidence of infection. Which of the following mechanisms most likely explains her immunity?

- A. Activated CD8⁺ T-lymphocyte–mediated clearance (42%)
- B. Disrupted replication of the viral genome (4%)
- C. Expression of interferon from infected cells (3%)
- ✓ D. Impaired virion entry into hepatocytes (47%)
- E. Reduced assembly of virions within the cytosol (1%)

Omitted
Correct answer
D

47%
Answered correctly

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Time Spent

02/19/2020
Last Updated

Explanation

Serologic evidence of **hepatitis B virus** (HBV) exposure is present in approximately 2 billion people worldwide. Nearly 250 million of these individuals have chronic infection and can transmit the virus to others. Perinatal transmission is most common in high prevalence countries (eg, sub-Saharan Africa); unprotected sex or intravenous drug use causes most infections in low-incidence countries (eg, United States). **Health care providers** are at **high risk** for infection due to potential exposure to the blood of infected patients.

HBV **vaccination** is recommended for all health care providers and other high-risk individuals (eg, intravenous drug users). The vaccine utilizes

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HBV **vaccination** is recommended for all health care providers and other high-risk individuals (eg, intravenous drug users). The vaccine utilizes **recombinant HBsAg** to generate protective immunity against the virus. HBsAg is a collection of envelope glycoproteins found on the surface of HBV; these glycoproteins mediate attachment of the virus to hepatocytes and subsequent viral entry. Patients who adequately respond to the HBV vaccine generate **anti-HBs antibodies**, which bind to circulating viral particles and prevent attachment to and penetration of hepatocytes.

Patients who have been immunized against HBV as well as those who have cleared the virus after acute infection will have anti-HBs antibodies. These 2 populations are distinguished by the presence of anti-HBc antibodies, which are seen only in those who have been exposed to the virus (not in immunized patients).

(Choice A) The immunity conferred by the hepatitis B vaccination is mediated by protective antibodies against HBsAg; the protective effects are not due to activation of cytotoxic T cells. However, in patients exposed to HBV, the resolution of acute infection is mediated primarily by a vigorous, polyclonal cytotoxic T-cell response that destroys infected hepatocytes.

(Choice B) HIV treatment often includes nucleotide and non-nucleoside reverse transcriptase inhibitors, which disrupt viral genome replication. Hepatitis C virus is often treated with similar medications (eg, sofosbuvir) that target viral RNA-dependent RNA polymerase. Immunization against HBV does not interfere with replication of the HBV genome.

(Choice C) HBV is considered a stealth virus because it possesses virulence factors that block portions of the innate immune system, including the release of interferon-gamma from infected cells. However, HBV immunization does not significantly affect the innate immune system.

(Choice E) NS5A inhibitors (eg, ledipasvir) are thought to block hepatitis C virus replication and assembly. HBV immunization generates protective antibodies against the HBsAg; it does not affect viral assembly.

Educational objective:

(not in immunized patients).

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Educational objective:
Immunization against hepatitis B virus uses recombinant HBsAg to generate anti-HBs antibodies. These antibodies prevent infection by binding to the envelope of circulating virus and inhibiting viral entry.

References

- Novel mechanism of antibodies to hepatitis B virus in blocking viral particle release from cells.
- Hepatitis B: the virus and disease.
- Pathogenesis of hepatitis B virus infection.

Immunology	Infectious Diseases	Hepatitis b
Subject	System	Topic

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A 22-year-old woman comes to the office because of a 6-month history of increasing neck and low back pain that is most severe in the morning. Her pain improves as the day passes. The patient has no history of trauma, rashes, or urinary symptoms. Vital signs are within normal limits. Examination shows tenderness over the lumbosacral area and at the insertion site of the Achilles tendon. Forward flexion is reduced. This patient's symptoms are most likely attributable to upregulation of which of the following cytokines?

A. IL-2 and interferon gamma

B. IL-4 and interferon alpha

C. IL-5 and tumor necrosis factor-alpha

D. IL-10 and transforming growth factor-beta

E. IL-17 and tumor necrosis factor-alpha

Submit

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A. IL-2 and interferon gamma (29%)
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C. IL-5 and tumor necrosis factor-alpha (11%)
D. IL-10 and transforming growth factor-beta (9%)
✓ E. IL-17 and tumor necrosis factor-alpha (44%)

Omitted
Correct answer
E

44%
Answered correctly

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Time Spent

06/18/2020
Last Updated

Explanation

Ankylosing spondylitis	
Pathogenesis	• Altered gut biome/defective mucosal barrier • Increased production of IL-17, TNF-α & prostaglandins • Increased risk with HLA-B27

Ankylosing spondylitis	
Pathogenesis	• Altered gut biome/defective mucosal barrier • Increased production of IL-17, TNF-α & prostaglandins • Increased risk with HLA-B27

Clinical findings	• Inflammatory back & buttock pain
	  ◦ Insidious onset at age <40
	  ◦ Relieved with exercise but not rest
	  ◦ Nocturnal pain
	• Reduced chest expansion & spinal mobility
	• Enthesitis (tenderness at tendon insertion sites)
	• Dactylitis (swelling of fingers & toes)
	• Anterior uveitis

Laboratory/imaging	• Elevated ESR & CRP • Sacroiliitis: bone erosions, subchondral sclerosis, eventual bony fusion (ankylosis) • Bridging syndesmophytes: ossification at vertebral body margins (bamboo spine)

HLA-B27 = human leukocyte antigen B27; **TNF-α** = tumor necrosis factor-alpha; **CRP** = C-reactive protein; **ESR** = erythrocyte sedimentation rate.

This patient with **inflammatory back pain** (ie, age <40, insidious onset, worse with rest/better with activity) and **enthesitis** (ie, tenderness at insertion of tendons/ligaments on bone) most likely has **ankylosing spondylitis** (AS). AS is characterized by bridging syndesmophytes in the vertebral column and ankylosis (bony fusion) of the apophyseal and sacroiliac joints.

AS is an inflammatory disorder thought to **originate largely in the gut**:

- Defects in the mucosal barrier and an abnormal intestinal microbiome induce an IL-17–mediated inflammatory response via innate lymphoid cells and T helper cells (eg, Th1, Th17). The risk is greater in individuals with human leukocyte antigen B27 **(HLA-B27)**, likely due to altered

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- **IL-17** stimulates production of additional inflammatory factors, primarily tumor necrosis factor-alpha (**TNF-alpha**) and **prostaglandins**, which have synergistic effects with IL-17 and induce **bony erosions** and **abnormal bone regrowth**.

Skeletal manifestations of AS occur primarily at **sites of mechanical stress**, such as the entheses, likely due to the migration of activated immune cells to these areas. Treatment options include nonsteroidal anti-inflammatory drugs (eg, ibuprofen, naproxen), which inhibit prostaglandin formation, and anti-TNF-alpha (eg, etanercept, infliximab) and anti–IL-17 (eg, secukinumab) agents.

(Choice A) IL-2 and interferon gamma have broad immune functions, including activation of the response against viruses and mycobacteria. Both cytokines inhibit Th17 cell differentiation and do not have a significant role in the pathogenesis of AS.

(Choice B) IL-4 is important in the differentiation of naïve Th cells into the Th2 subset, alternative macrophage activation (M2 type), and IgE production. It may also have a protective role in AS by limiting IL-17 production by Th1 and Th17 cells. Interferon alpha is involved primarily in antiviral activity and is not a significant factor in the pathogenesis of AS.

(Choice C) IL-5 induces B-cell growth, IgA production, and eosinophil activity. IL-5 and IL-4 are important in the etiology of certain allergic disorders (eg, allergic rhinitis, asthma), but do not contribute significantly to AS.

(Choice D) IL-10 is an antiinflammatory cytokine. Transforming growth factor-beta has antiinflammatory and profibrotic effects. These cytokines have only a minor effect in AS.

Educational objective:

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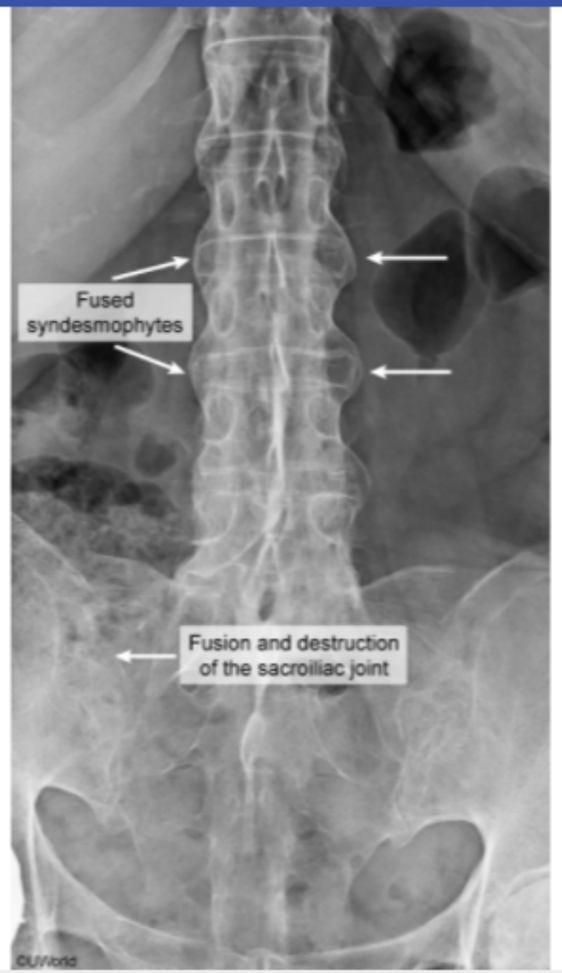

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- **IL-17** stimulates production of additional inflammatory factors, primarily tumor necrosis factor-alpha (**TNF-alpha**) and **prostaglandins**, which have synergistic effects with IL-17 and induce **bony erosions** and **abnormal bone regrowth**.

Skeletal manifestations of AS occur primarily at **sites of mechanical stress**, such as the entheses, likely due to the migration of activated immune cells to these areas. Treatment options include nonsteroidal anti-inflammatory drugs (eg, ibuprofen, naproxen), which inhibit prostaglandin formation, and anti-TNF-alpha (eg, etanercept, infliximab) and anti–IL-17 (eg, secukinumab) agents.

(Choice A) IL-2 and interferon gamma have broad immune functions, including activation of the response against viruses and mycobacteria. Both cytokines inhibit Th17 cell differentiation and do not have a significant role in the pathogenesis of AS.

(Choice B) IL-4 is important in the differentiation of naïve Th cells into the Th2 subset, alternative macrophage activation (M2 type), and IgE production. It may also have a protective role in AS by limiting IL-17 production by Th1 and Th17 cells. Interferon alpha is involved primarily in antiviral activity and is not a significant factor in the pathogenesis of AS.

(Choice C) IL-5 induces B-cell growth, IgA production, and eosinophil activity. IL-5 and IL-4 are important in the etiology of certain allergic disorders (eg, allergic rhinitis, asthma), but do not contribute significantly to AS.

(Choice D) IL-10 is an antiinflammatory cytokine. Transforming growth factor-beta has antiinflammatory and profibrotic effects. These cytokines have only a minor effect in AS.

Educational objective:
The pathogenesis of ankylosing spondylitis likely originates with defects in the intestinal mucosal barrier and exposure to the gut microbiome that lead to an enhanced IL-17–mediated inflammatory response. IL-17 stimulates production of additional inflammatory factors, primarily tumor necrosis factor-alpha and prostaglandins, which have synergistic proinflammatory effects and induce bony erosions and abnormal bone regrowth in the skeleton.

Immunology	Rheumatology/Orthopedics & Sports	Ankylosing spondylitis
Subject	System	Topic

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A 34-year-old man is brought to the hospital by ambulance after being involved in a motor vehicle collision. He was an unrestrained passenger and sustained considerable trauma. On arrival to the emergency department, he is hypotensive and bleeding from several sites. The patient receives an emergency blood transfusion as part of the resuscitation efforts. Abdominal ultrasound reveals splenic laceration and blood in the peritoneal cavity. En route to the operating room, the patient develops difficulty breathing, chills, and pain in the chest and back. Urine drainage from the Foley catheter was initially clear but now appears brown in color. Which of the following is the most likely cause of this patient's new findings?

A. $CD8^+$ lymphocyte-mediated cytotoxicity

B. Complement-mediated cell lysis

C. Endotoxin-induced TNF-α surge

D. IgE-mediated reaction to serum proteins

E. Vascular deposition of immune complexes

Submit

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- A. $CD8^+$ lymphocyte-mediated cytotoxicity (9%)
- ✓ B. Complement-mediated cell lysis (50%)
- C. Endotoxin-induced TNF-α surge (8%)
- D. IgE-mediated reaction to serum proteins (18%)
- E. Vascular deposition of immune complexes (13%)

Omitted
Correct answer
B

50%
Answered correctly

02 secs
Time Spent

06/21/2020
Last Updated

Explanation

Hypersensitivity reactions			
	Humoral	Cellular	Examples

Hypersensitivity reactions			
	Humoral components	**Cellular components**	**Examples**
Type I (immediate)	• **IgE**	• Basophils • Mast cells	• Anaphylaxis • Allergies
Type II (cytotoxic)	• **IgG & IgM** autoantibodies • Complement activation	• NK cells • Eosinophils • Neutrophils • Macrophages	• Autoimmune hemolytic anemia • Goodpasture syndrome
Type III (immune complex)	• Deposition of **antibody-antigen complexes** • Complement activation	• Neutrophils	• Serum sickness • PSGN • Lupus nephritis
Type IV (delayed type)	• None	• **T cells** • **Macrophages**	• Contact dermatitis • Tuberculin skin test

NK = natural killer; **PSGN** = poststreptococcal glomerulonephritis.

This patient is most likely experiencing an **acute hemolytic transfusion reaction**. This condition presents with **fever and chills**, hypotension, dyspnea, **chest and/or back pain**, and **hemoglobinuria** (red- to brown-colored urine). Patients may also develop disseminated intravascular coagulation and renal failure. Acute hemolytic reactions occur within **minutes to hours** of starting a blood transfusion and are most often due to ABO incompatibility between the donor and recipient. These reactions can be fatal and require **immediate cessation** of the transfusion when the diagnosis is suspected.

Acute hemolytic transfusion reactions are an example of an antibody-mediated (type II) hypersensitivity reaction. Anti-ABO antibodies (mainly

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Acute hemolytic transfusion reactions are an example of an **antibody-mediated (type II)** hypersensitivity reaction. Anti-ABO antibodies (mainly IgM) in the recipient bind the corresponding antigens on transfused donor erythrocytes, leading to complement activation. Anaphylatoxins (C3a and C5a) cause vasodilatation and symptoms of shock, while formation of the membrane attack complex (C5b-C9) leads to **complement-mediated cell lysis**. Hemolytic disease of the newborn due to Rh-incompatibility is another example of type II hypersensitivity.

(Choice A) Cytotoxic $CD8^+$ T-lymphocytes are responsible for destroying cells infected with intracellular pathogens (eg, viruses). Recognition of an antigen-MHC class I complex by the T-cell receptor activates $CD8^+$ lymphocytes, which then initiate apoptosis of the infected cell.

(Choice C) TNF-α is produced by macrophages in response to bacterial endotoxin and causes symptoms of septic shock (eg, fever, hypotension, and tachycardia) when released in large amounts. Transfusion transmitted bacterial infection could cause septic shock, but it would not result in hemoglobinuria.

(Choice D) Allergic transfusion reactions are IgE-mediated (type I) hypersensitivity reactions against plasma proteins found in transfused blood. They can be mild (urticaria, itching) or result in severe anaphylaxis (most common in IgA-deficient patients with anti-IgA antibodies).

(Choice E) Vascular deposition of immune complexes is an example of type III hypersensitivity. In conditions such as systemic lupus erythematosus and rheumatoid arthritis, antigen-antibody complexes deposit in various tissues and activate complement, causing tissue inflammation and destruction.

Educational objective:
Acute hemolytic transfusion reaction is a antibody-mediated (type II) hypersensitivity reaction caused by pre-existing anti-ABO antibodies that bind antigens on transfused donor erythrocytes. Subsequent complement activation results in erythrocyte lysis, vasodilation, and symptoms of shock. Common findings include fever, hypotension, chest and back pain, and hemoglobinuria.

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Immunology	Hematology & Oncology	Hypersensitivity reactions
Subject	System	Topic

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A 40-year-old woman, gravida 4 para 4, comes to the clinic due to anemia. A week ago, the patient was seen in the emergency department due to fatigue, shortness of breath, and increasingly heavy, irregular menses. Laboratory evaluation showed a hemoglobin level of 5.4 g/dL. After a transfusion with packed red blood cells, her follow-up hemoglobin level was 7.8 g/dL prior to discharge. Since then, the patient's energy and breathing have improved, and she has had no further menstrual bleeding. However, yellowing of the eyes and face has developed over the last day. Vital signs are normal. Examination reveals scleral icterus. There is no hepatosplenomegaly. Laboratory results are as follows:

Complete blood count

Hemoglobin	5.9 g/dL
Reticulocytes	7%

Liver function study

Total bilirubin	3.8 mg/dL

This patient's current symptoms are most likely due to which of the following antibody-antigen reactions?

A. Blood product antibodies against the patient's ABO-group antigen

B. Blood product antibodies against the patient's minor red blood cell antigen

C. Patient's antibodies against the blood product ABO-group antigen

D. Patient's antibodies against the blood product IgA

E. Patient's antibodies against the blood product minor red blood cell antigen

Submit

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Hemoglobin	5.9 g/dL
Reticulocytes	7%

Liver function study

Total bilirubin	3.8 mg/dL

This patient's current symptoms are most likely due to which of the following antibody-antigen reactions?

A. Blood product antibodies against the patient's ABO-group antigen (5%)

B. Blood product antibodies against the patient's minor red blood cell antigen (7%)

C. Patient's antibodies against the blood product ABO-group antigen (27%)

D. Patient's antibodies against the blood product IgA (10%)

✓ E. Patient's antibodies against the blood product minor red blood cell antigen (49%)

Omitted
Correct answer

49%
Answered correctly

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Time Spent

02/01/2020
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Immunologic blood transfusion reactions

Transfusion reaction	Onset	Cause	Key features
Allergic	Minutes to hours	Preformed antibodies against blood product component	• Minor: urticaria • Major: anaphylaxis (eg, IgA-deficient recipient)
Acute hemolytic	Minutes to hours	ABO incompatibility (often clerical error)	• Fever, flank pain, hemoglobinuria • DIC • + Coombs test
Febrile nonhemolytic (most common)	Hours	Cytokine accumulation during blood storage	• Fever & chills
Transfusion-related acute lung injury	Hours	Donor antileukocyte antibodies	• Respiratory distress • Bilateral pulmonary edema
Delayed hemolytic	Days to weeks	Anamnestic antibody response	• Often asymptomatic • Laboratory evidence of hemolytic anemia • + Coombs test

DIC = disseminated intravascular coagulation.

This patient has jaundice and hemolytic anemia a week after a transfusion, findings suggestive of a **delayed hemolytic transfusion reaction** (DHTR). This reaction occurs in patients who were **previously exposed** to a foreign, **minor red blood cell (RBC) antigen** (non-ABO) via mechanisms such as pregnancy, prior transfusion, or intravenous drug use. During the first exposure, only a low, typically undetectable, antibody

This patient has jaundice and hemolytic anemia a week after a transfusion, findings suggestive of a **delayed hemolytic transfusion reaction** (DHTR). This reaction occurs in patients who were **previously exposed** to a foreign, **minor red blood cell (RBC) antigen** (non-ABO) via mechanisms such as pregnancy, prior transfusion, or intravenous drug use. During the first exposure, only a low, typically undetectable, antibody response is initially mounted. On **reexposure** via transfusion, the patient's memory B cells produced a larger surge of antibodies, resulting in detectable hemolysis. This is known as an **anamnestic response**.

DHTR is usually **mild** and develops **>24 hours after transfusion**, most commonly after 1-2 weeks. Most patients are asymptomatic and diagnosed only after findings of a newly positive direct antibody **(+ Coombs)** test and antibody screen. Additional laboratory findings include anemia with compensatory reticulocytosis and evidence of hemolysis (eg, ↑ indirect bilirubin, ↑ lactate dehydrogenase).

(Choices A and B) Mild hemolysis can result from the transfusion of plasma products (eg, fresh frozen plasma, platelets), which can contain donor antibodies that target ABO or minor antigens on recipient RBCs. This reaction does not typically occur with the transfusion of packed RBCs, which this patient received, because RBCs are removed from the plasma layer and washed during the blood-separation process.

(Choice C) An acute hemolytic transfusion reaction is caused by ABO incompatibility (eg, due to clerical error). Patients naturally have preformed antibodies against foreign ABO antigens (eg, anti-B antibodies in a type A patient) that will attack antigens on mismatched donor RBCs (eg, type B donor blood). Massive hemolysis occurs within minutes to hours of transfusion, causing fever, flank pain, and hemoglobinuria.

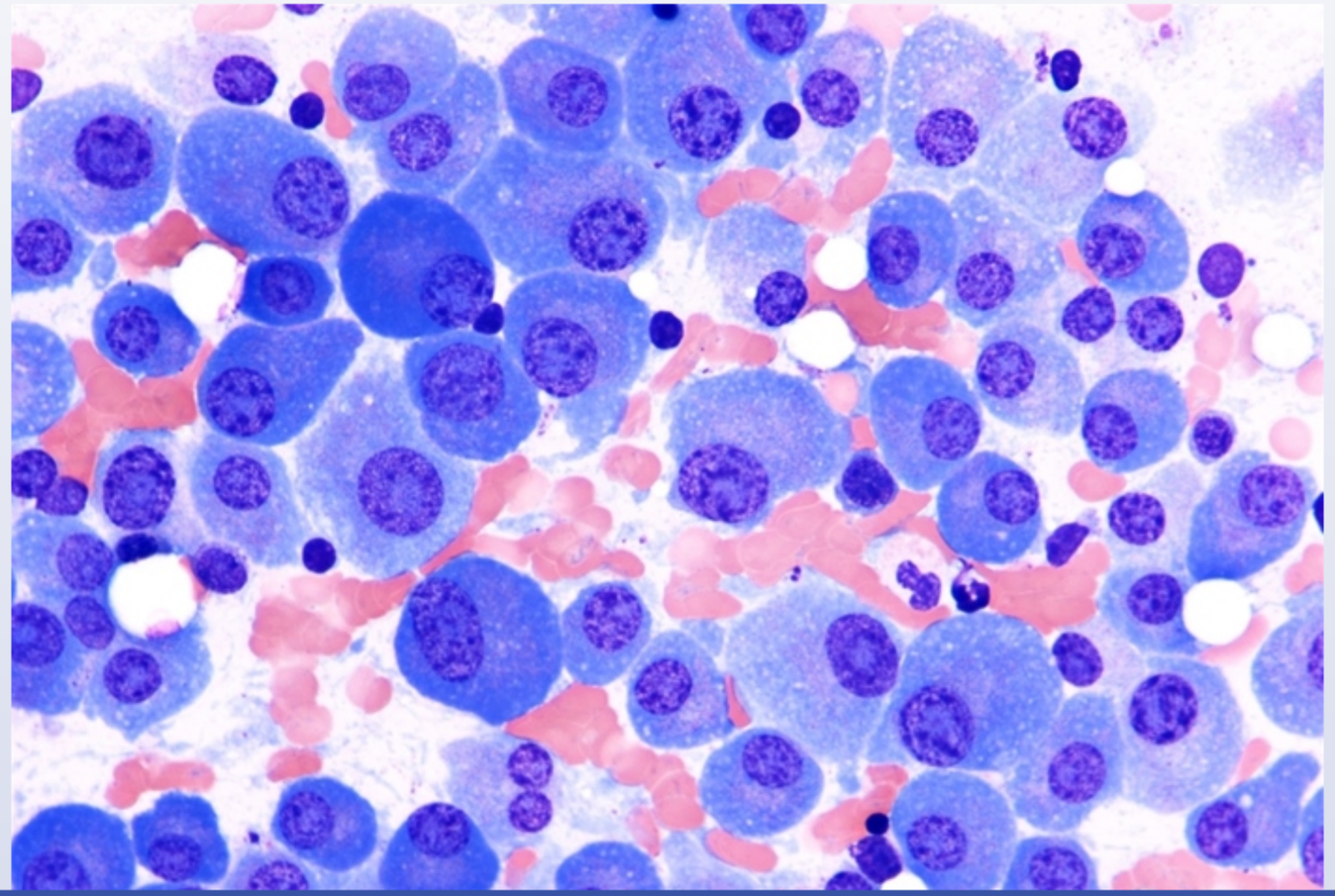
(Choice D) Anaphylactic transfusion reactions occur within minutes of transfusion initiation and present with wheezing, angioedema, and hypotension, findings not seen in this patient. This reaction can occur in patients with IgA deficiency due to the reaction of recipient anti-IgA antibodies against donor IgA.

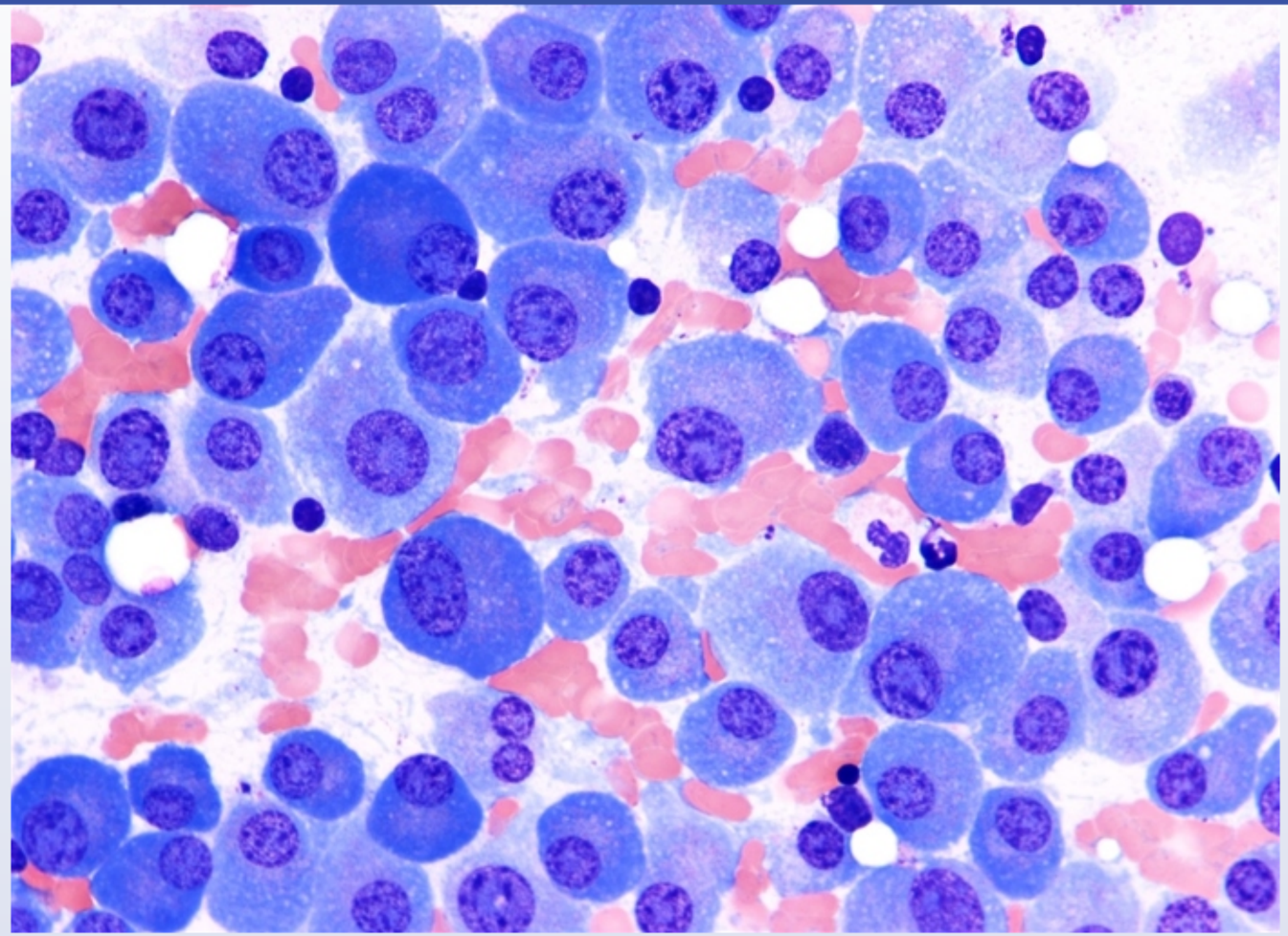
Educational objective:
Delayed hemolytic transfusion reactions are usually mild, hemolytic reactions that occur >24 hours after blood transfusion. They are a type of anamnestic response (delayed immunologic response) that occurs in patients previously exposed to a minor RBC antigen (eg, previous blood transfusion, pregnancy).

References

- Transfusion reactions.

A 68-year-old woman comes to the office due to recurrent bacterial sinusitis, pneumonia, and urinary tract infections over the past several months. The patient has no prior medical conditions or history of severe infections in childhood. She does not use tobacco, alcohol, or illicit drugs. Temperature is 36.6 C (97.9 F), blood pressure is 130/76 mm Hg, and pulse is 72/min. On physical examination, the lungs are clear to auscultation, heart sounds are normal, and the abdomen is soft and nontender with no hepatosplenomegaly. Laboratory testing reveals normocytic normochromic anemia. Bone marrow aspirate shows an increased number of cells, as shown below.

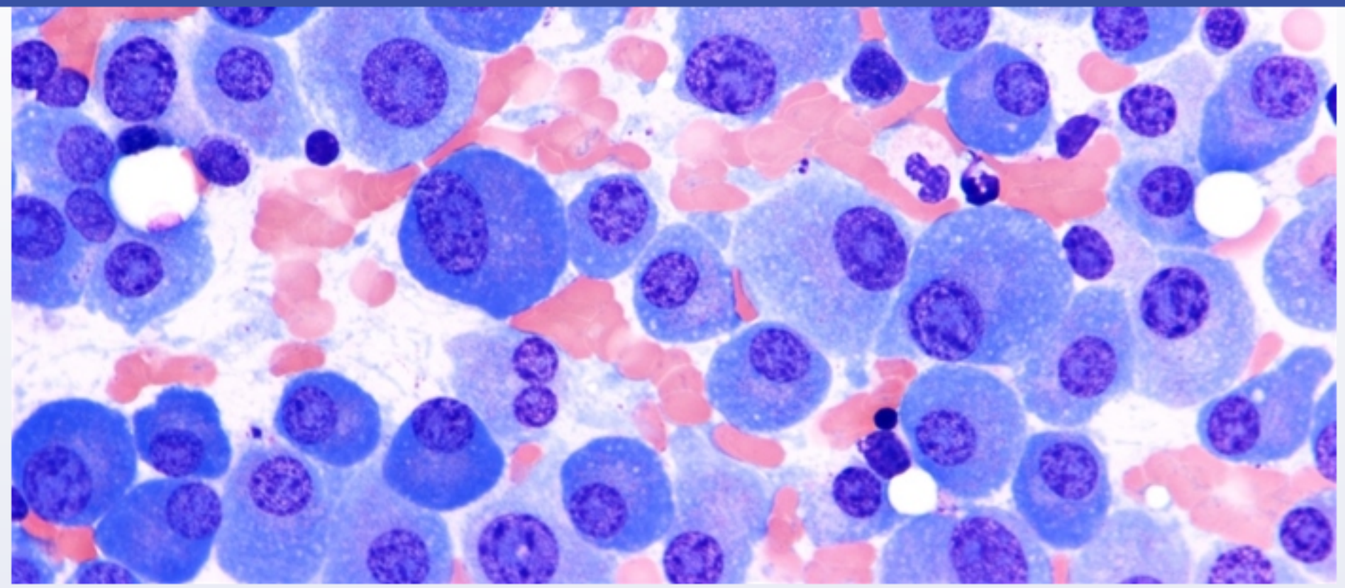




Which of the following is the most likely cause of this patient's increased susceptibility to infections?

A. Aberrant lysosomal transport and fusion in leukocytes

B. Decreased production of functional immunoglobulins



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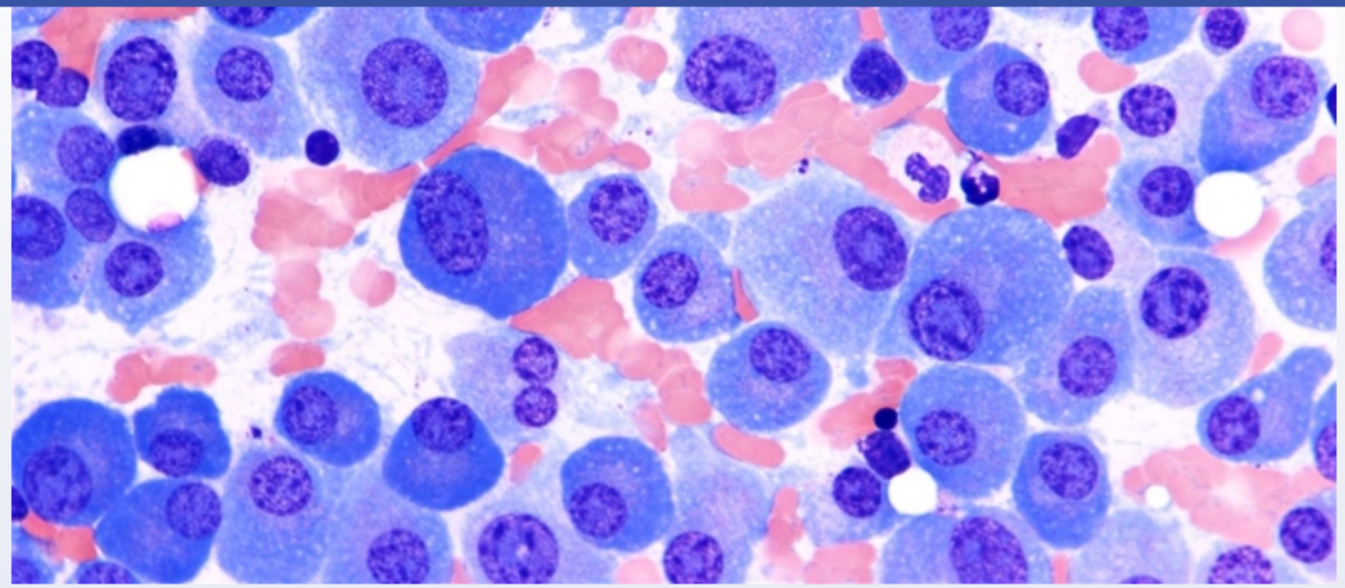
- A. Aberrant lysosomal transport and fusion in leukocytes
- B. Decreased production of functional immunoglobulins
- C. Defective adhesion and transmigration of leukocytes
- D. Impaired formation of membrane attack complex
- E. Impaired phagocytic ability to generate superoxide

Submit



Which of the following is the most likely cause of this patient's increased susceptibility to infections?

- A. Aberrant lysosomal transport and fusion in leukocytes (6%)
- ✓ B. Decreased production of functional immunoglobulins (77%)
- C. Defective adhesion and transmigration of leukocytes (7%)
- D. Impaired formation of membrane attack complex (2%)
- E. Impaired phagocytic ability to generate superoxide (5%)

Omitted
Correct answer

77%
Answered correctly

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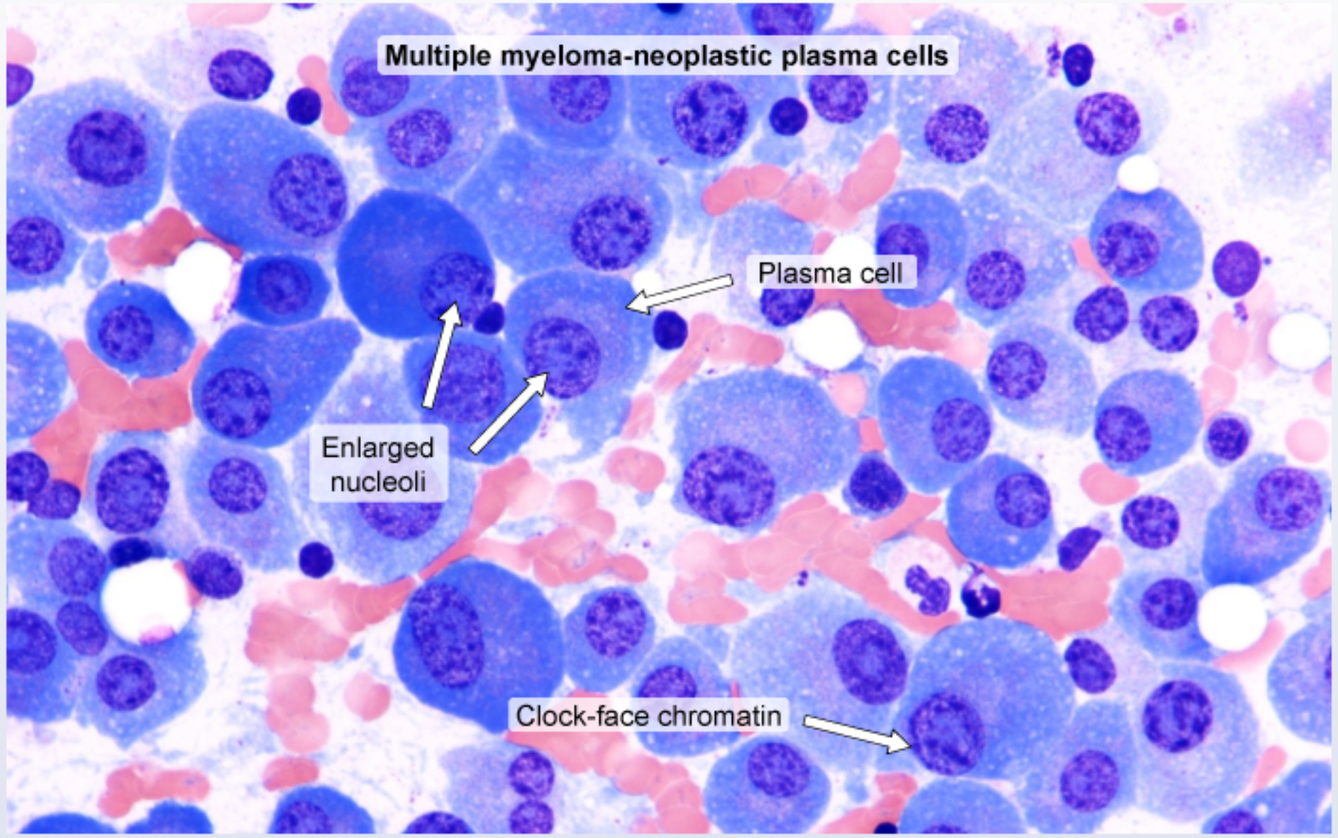
Explanation



This patient's bone marrow aspirate has numerous **plasma cells**, which are distinguished by the presence of abundant basophilic cytoplasm, **perinuclear paleness** (large Golgi apparatus), and nuclei with "**clock-face**" (peripheral) chromatin. The presence of >10% plasma cells in the bone marrow raises strong suspicion for **multiple myeloma** (MM).

In MM, neoplastic plasma cells crowd the bone marrow, leading to impairments in normal hematopoiesis. B-cell development is particularly affected, which reduces plasma cell diversity and **limits the generation of targeted immunoglobulins** against infectious agents. Therefore,

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In MM, neoplastic plasma cells crowd the bone marrow, leading to impairments in normal hematopoiesis. B-cell development is particularly affected, which reduces plasma cell diversity and **limits the generation of targeted immunoglobulins** against infectious agents. Therefore, patients with MM have increased risk of **recurrent bacterial infections**, particularly of the urinary tract, lungs, and sinuses. Although patients with MM have high levels of circulating monoclonal immunoglobulin, monoclonal immunoglobulin does not provide immunity against a diverse range of pathogens.

MM is also associated with normocytic anemia (due to ineffective erythropoiesis), bone pain (due to osteolytic lesions), hypercalcemia, and renal insufficiency (due to clogging of the tubules with immunoglobulin light chains).

(Choice A) Chediak-Higashi syndrome is a rare autosomal recessive disorder that causes abnormal lysosomal fusion and transport. Although it is associated with recurrent bacterial infections and hematologic malignancies, most cases are identified in early childhood, and patients generally have hypopigmentation and progressive neurologic dysfunction.

(Choice C) Leukocyte adhesion deficiency is an inherited disorder associated with defective adhesion and transmigration of leukocytes from the vasculature to tissues. Patients typically have recurrent bacterial infections that begin in early childhood. It is not associated with excessive plasma cells in the bone marrow.

(Choice D) Terminal complement deficiency (C5-C9) prevents the formation of the membrane attack complex and dramatically increases the risk of recurrent infection with *Neisseria* species; patients are usually healthy otherwise and have no abnormalities in the bone marrow.

(Choice E) Chronic granulomatous disease is a genetic disorder associated with severe bacterial and fungal infections due to impaired ability of phagocytes to generate reactive oxygen species (oxidative burst). Most cases present in early childhood, and plasma cell effacement of the bone marrow would not be seen.

Educational objective:
Multiple myeloma is associated with the clonal proliferation of plasma cells in the bone marrow. This prevents normal B-cell lymphogenesis and

patients with MM have increased risk of **recurrent bacterial infections**, particularly of the urinary tract, lungs, and sinuses. Although patients with MM have high levels of circulating monoclonal immunoglobulin, monoclonal immunoglobulin does not provide immunity against a diverse range of pathogens.

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Educational objective:
Multiple myeloma is associated with the clonal proliferation of plasma cells in the bone marrow. This prevents normal B-cell lymphogenesis and increases the risk of bacterial infection due to decreased production of normal immunoglobulins.

Immunology	Hematology & Oncology	Multiple myeloma
Subject	System	Topic

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A 24-year-old recent Russian immigrant describes a long history of weight loss, night sweats and nagging cough. Imaging and biopsy of his lungs reveal numerous apical granulomas with central caseous necrosis. Surrounding the necrotic areas are large cells with abundant pale cytoplasm. Which of the following surface markers is most specific for those cells?

- A. CD4
- B. CD7
- C. CD8
- D. CD14
- E. CD20

Submit

A 24-year-old recent Russian immigrant describes a long history of weight loss, night sweats and nagging cough. Imaging and biopsy of his lungs reveal numerous apical granulomas with central caseous necrosis. Surrounding the necrotic areas are large cells with abundant pale cytoplasm. Which of the following surface markers is most specific for those cells?

- A. CD4 (21%)
- B. CD7 (2%)
- C. CD8 (10%)
- ✓ D. CD14 (52%)
- E. CD20 (12%)

Omitted
Correct answer
D

52%
Answered correctly

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04/21/2020
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Explanation

This patient's history of night sweats, weight loss, and cough with the finding of apical pulmonary granulomas showing caseous necrosis is highly suggestive of **active tuberculosis**. The **caseating granulomas** of tuberculosis consist of **large epithelioid macrophages** with pale pink granular cytoplasm surrounding a central region of **necrotic debris**. The most specific cell surface marker of the monocyte-macrophage cell lineage is **CD14**, which binds to bacterial lipopolysaccharide.

(Choice A) Together with T cell receptors, CD4 transmembrane proteins recognize antigens presented by MHC Class II molecules. CD4 is expressed on the surface of macrophages but is also found on T helper cells. Therefore, CD4 is not a specific marker for

D

Explanation

This patient's history of night sweats, weight loss, and cough with the finding of apical pulmonary granulomas showing caseous necrosis is highly suggestive of **active tuberculosis**. The **caseating granulomas** of tuberculosis consist of **large epithelioid macrophages** with pale pink granular cytoplasm surrounding a central region of **necrotic debris**. The most specific cell surface marker of the monocyte-macrophage cell lineage is **CD14**, which binds to bacterial lipopolysaccharide.

(Choice A) Together with T cell receptors, CD4 transmembrane proteins recognize antigens presented by MHC Class II molecules. CD4 is expressed on the surface of macrophages but is also found on T helper cells. Therefore, CD4 is not a specific marker for monocytes/macrophages.

(Choice B) CD7 is a multi-chain complex T cell marker. It is key to the interaction between T cells and B cells during lymphoid cell development.

(Choice C) CD8 is a transmembrane protein associated with T cell receptors and found on the surface of cytotoxic T cells. Together, these proteins recognize antigenic peptides presented by MHC Class I molecules.

(Choice E) CD20 is a B cell surface marker. Monoclonal antibodies against the CD-20 antigen (Rituximab) have been successful in the treatment of lymphomas.

Educational Objective:
The caseating granulomas of tuberculosis are almost always surrounded by large epithelioid macrophages with pale pink granular cytoplasm. CD14 is a surface marker specific to the monocyte-macrophage cell lineage.

Immunology	Hematology & Oncology	Tuberculosis
Subject	System	Topic

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A 1-year-old boy is brought to the clinic after suffering repeated infections over the last 4 months, including otitis media, pneumonia, and erysipelas. Although his infections have been responsive to treatment, his father says, "My son is constantly on antibiotics. I'm afraid he will end up like his uncle who passed away from pneumonia as a teenager." The patient also has persistent diarrhea, and a recent stool antigen detection assay was positive for *Giardia lamblia*. His complete blood count is normal, but immunoglobulin panel demonstrates very low serum levels of all immunoglobulin types. Intradermal injection of *Candida* antigens results in a large indurated nodule within 48 hours. This patient's lymph nodes most likely lack which of the following structures?

A. Germinal centers
B. Outer cortex
C. Paracortical zone
D. Subcapsular sinuses
E. Trabeculae

Submit

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- ✓ A. Germinal centers (79%)
- B. Outer cortex (6%)
- C. Paracortical zone (12%)
- D. Subcapsular sinuses (0%)
- E. Trabeculae (0%)

Omitted
Correct answer
A

79%
Answered correctly

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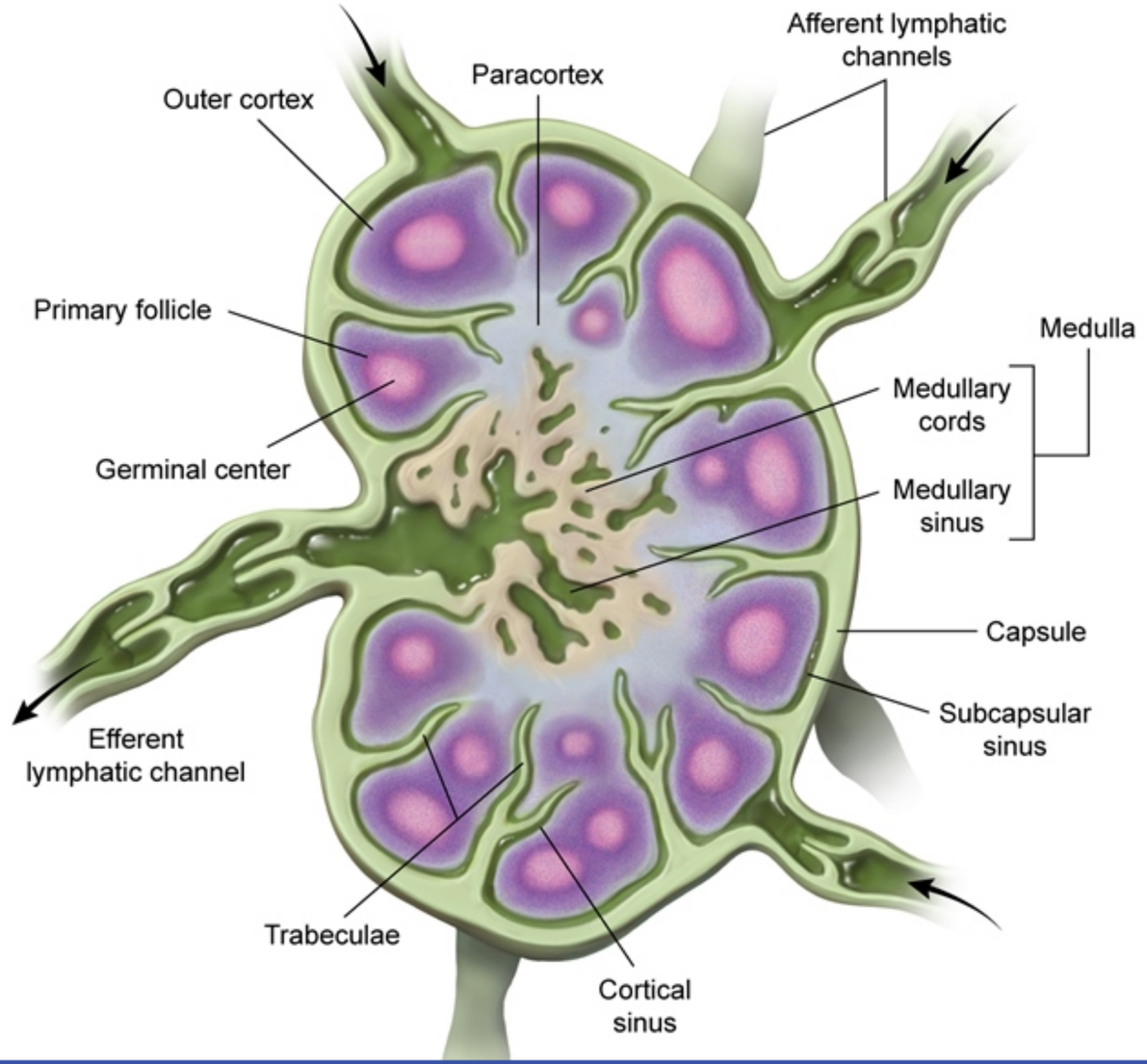
Explanation

Lymph node anatomy

Afferent lymphatic

Lymph node anatomy



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This patient's recurrent infections in the setting of intact T lymphocyte function (positive response to *Candida* antigens) and **very low immunoglobulin levels** are suggestive of **X-linked agammaglobulinemia** (XLA). This condition results from a mutation in the **Bruton tyrosine kinase** gene that causes failure of bone marrow pre-B cells to develop into mature B lymphocytes. As a result, patients have very low or absent numbers of B lymphocytes in the peripheral blood and lymphoid tissues.

B lymphocytes normally aggregate in the cortex of lymph nodes to form lymphoid follicles. Primary follicles are dense and dormant; secondary follicles have a pale germinal center containing proliferating B cells in response to an antigenic stimulus. In agammaglobulinemia, **germinal centers** and primary lymphoid follicles do not form due to an **absence of B cells**.

(Choice B) The outer cortex is composed of primary and secondary lymphoid follicles (B cell-rich regions), but it also contains prominent numbers of CD4+ T cells within the interfollicular regions (allowing for T-B cell interaction). In patients with agammaglobulinemia, the outer cortex is present but diminished.

(Choice C) The paracortical zone lies internal to the cortex of the lymph node. This zone is populated primarily by T lymphocytes and dendritic cells. Dendritic cells present antigens collected from the blood and lymph to the T lymphocytes aggregated in this section of the node. This patient's positive reaction to *Candida* antigens (type 4 hypersensitivity) indicates intact T lymphocyte function.

(Choices D and E) The subcapsular sinuses are found between the capsule and the cortex of the lymph node and are in direct communication with afferent lymphatic vessels. These sinuses are connected to cortical sinuses that line the trabeculae and penetrate through the cortex and paracortex to reach the medulla. From there, medullary sinuses drain into the efferent lymphatic channel.

Educational objective:
X-linked (Bruton) agammaglobulinemia is caused by a defect in B cell maturation, resulting in the absence of mature B cells with severe deficiency of all immunoglobulin types. T cell numbers and function remain intact. Due to the absence of B cells, primary lymphoid follicles and germinal centers will not form within lymph nodes.

Immunology	Hematology & Oncology	X-linked agammaglobulinemia
Subject	System	Topic

A 12-month-old boy is evaluated for an eczematous rash. Medical history is significant for several severe respiratory infections that required hospitalization. Complete blood count shows white blood cells at 9,000/mm^3 and platelets at 40,000/mm^3. The platelets seem abnormally small and deformed on the peripheral blood smear. Which of the following is the most likely diagnosis?

- A. Aplastic anemia
- B. Ataxia telangiectasia syndrome
- C. Chédiak-Higashi syndrome
- D. DiGeorge syndrome
- E. Hemolytic uremic syndrome
- F. Wiskott-Aldrich syndrome

Submit

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- A. Aplastic anemia (4%)
- B. Ataxia telangiectasia syndrome (3%)
- C. Chédiak-Higashi syndrome (10%)
- D. DiGeorge syndrome (4%)
- E. Hemolytic uremic syndrome (5%)
- ✓ F. Wiskott-Aldrich syndrome (72%)

Omitted
Correct answer
F

72%
Answered correctly

02 secs
Time Spent

02/19/2020
Last Updated

Explanation

Distinctive features of selected primary immunodeficiency disorders	
Condition	Characteristic features

Distinctive features of selected primary immunodeficiency disorders

Condition	Characteristic features
Ataxia-telangiectasia	• Ataxia • Telangiectasias • Sinopulmonary infections
Chédiak-Higashi syndrome	• Oculocutaneous albinism • Pyogenic infections • Progressive neurologic dysfunction
Chronic granulomatous disease	• Severe bacterial & fungal infections • Granuloma formation
DiGeorge syndrome	• Congenital heart disease • Dysmorphic facies • Hypocalcemia
Severe combined immunodeficiency	• Severe bacterial & viral infections in infancy • Chronic diarrhea • Mucocutaneous candidiasis
Terminal complement deficiency	• Recurrent *Neisseria* infection

Exhibit Display

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Terminal complement deficiency	• Recurrent *Neisseria* infection
Wiskott-Aldrich syndrome	• Recurrent infections that worsen with age • Easy bleeding • Eczema

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DiGeorge syndrome	• Congenital heart disease • Dysmorphic facies • Hypocalcemia
Severe combined immunodeficiency	• Severe bacterial & viral infections in infancy • Chronic diarrhea • Mucocutaneous candidiasis
Terminal complement deficiency	• Recurrent *Neisseria* infection
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This patient has the 3 characteristic findings of **Wiskott-Aldrich syndrome** (WAS): **eczema**, recurrent infections, and **thrombocytopenia**. Because it is an **X-linked recessive** disorder, WAS manifests almost exclusively in males. It is caused by a mutation in cytoskeleton proteins that are critical for normal cell structure and the cell-to-cell interactions required for activation of hematologic cells (eg, platelets, immune cells).

In patients with WAS, platelets are both abnormally shaped and deficient, causing petechiae, purpura, hematemesis, and epistaxis that can be present at birth. A deficiency in B cells results in recurrent **pyogenic infections** due to an inability to mount a humoral immune response against organisms with a polysaccharide capsule (eg, *Neisseria meningitidis*, *Haemophilus influenzae*, *Streptococcus pneumoniae*). Patients also have T-cell deficiency, leading to infections with **opportunistic pathogens** (eg, *Pneumocystis jiroveci*). **Severe recurrent infections** develop after transplacental maternal IgG and maternal mucosal IgA are degraded around 6 months of age. Treatment is with HLA-matched bone marrow transplantation.

(Choice A) Aplastic anemia (ie, pancytopenia) classically results from ionizing radiation or the use of cytotoxic medications (eg, chemotherapeutic

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(Choice A) Aplastic anemia (ie, pancytopenia) classically results from ionizing radiation or the use of cytotoxic medications (eg, chemotherapeutic agents, chloramphenicol). Although aplastic anemia is associated with recurrent infections, abnormally shaped platelets and eczema are more characteristic of WAS.

(Choice B) Ataxia telangiectasia syndrome is associated with a deficiency of both B and T cells; however, patients characteristically have progressive ataxia and telangiectasia rather than eczema.

(Choice C) Patients with Chédiak-Higashi syndrome have coagulation defects and recurrent pyogenic infections due to the dysfunction of phagocyte phagosome-lysosome fusion. However, they also typically have oculocutaneous albinism, peripheral neuropathy, and giant cytoplasmic granules on peripheral blood smear.

(Choice D) DiGeorge syndrome results from maldevelopment of the third and fourth pharyngeal pouches, which causes hypoplasia of the parathyroid glands and thymus (T cell deficiency), cardiac and aortic arch abnormalities, and characteristic facies due to maldevelopment of the mandible.

(Choice E) Hemolytic uremic syndrome most often occurs in children after infection with Shiga toxin–producing *Escherichia coli*. Patients typically have thrombocytopenia with microangiopathic hemolytic anemia and acute renal failure.

Educational objective:

transplacental maternal IgG and maternal mucosal IgA are degraded around 6 months of age. Treatment is with HLA-matched bone marrow transplantation.

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Educational objective:
Wiskott-Aldrich syndrome is characterized by the triad of eczema, thrombocytopenia, and combined B and T cell deficiency. Patients can have thrombocytopenia at birth, with eczema and repeated infections due to encapsulated and/or opportunistic organisms usually developing later around 6 to 12 months of age.

Immunology	Hematology & Oncology	Wiskott-aldrich syndrome
Subject	System	Topic

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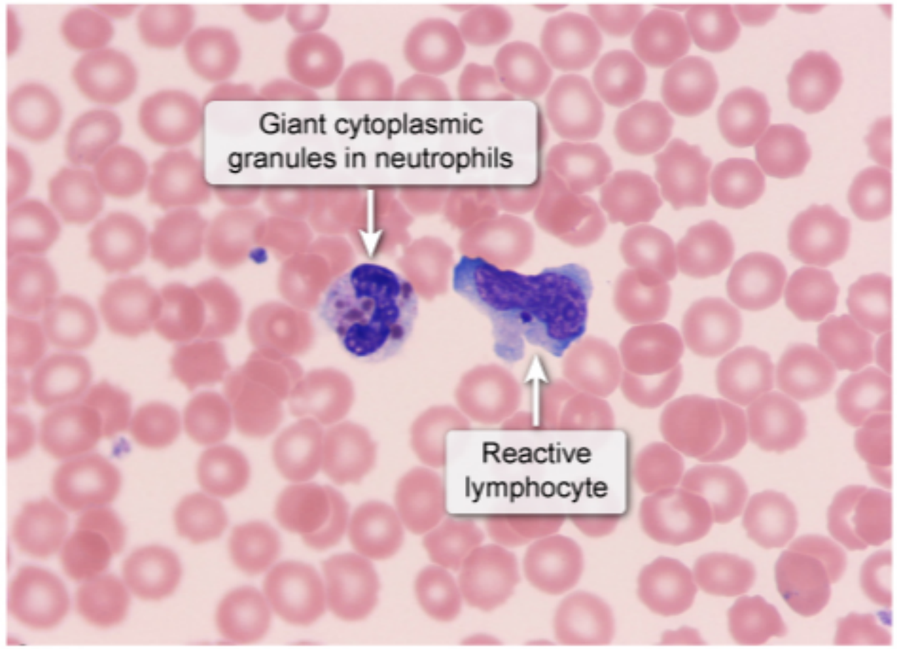
transplacental maternal IgG and maternal mucosal IgA are degraded around 6 months of age. Treatment is with HLA-matched bone marrow

Exhibit Display

Chédiak-Higashi syndrome



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A 28-year-old primigravid woman comes to the office for a routine prenatal checkup at 28 weeks gestation. The patient has no concerns and has had an uneventful pregnancy to date. Physical examination shows a uterine size concordant with ultrasound dates, and fetal cardiac activity is in the normal range. After reviewing the results of her laboratory evaluations, the physician administers an injection of anti-Rh(D) immunoglobulin. The administered antibodies most likely belong to which of the following immunoglobulin classes?

A. IgA
B. IgD
C. IgE
D. IgG
E. IgM

Submit

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- A. IgA (1%)
- B. IgD (2%)
- C. IgE (0%)
- ✓ D. IgG (72%)
- E. IgM (22%)

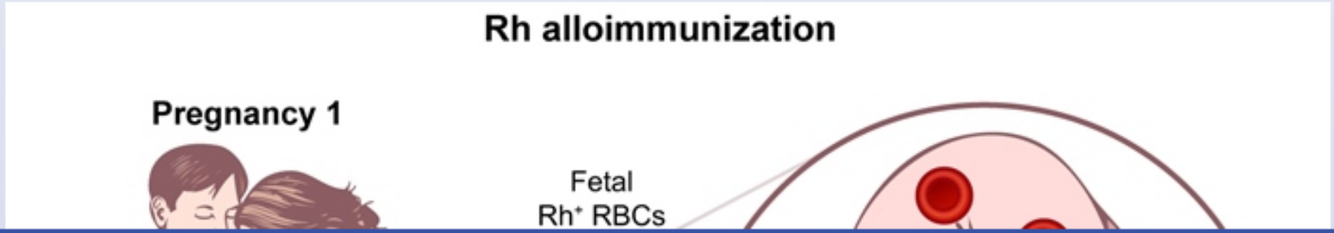
Omitted
Correct answer
D

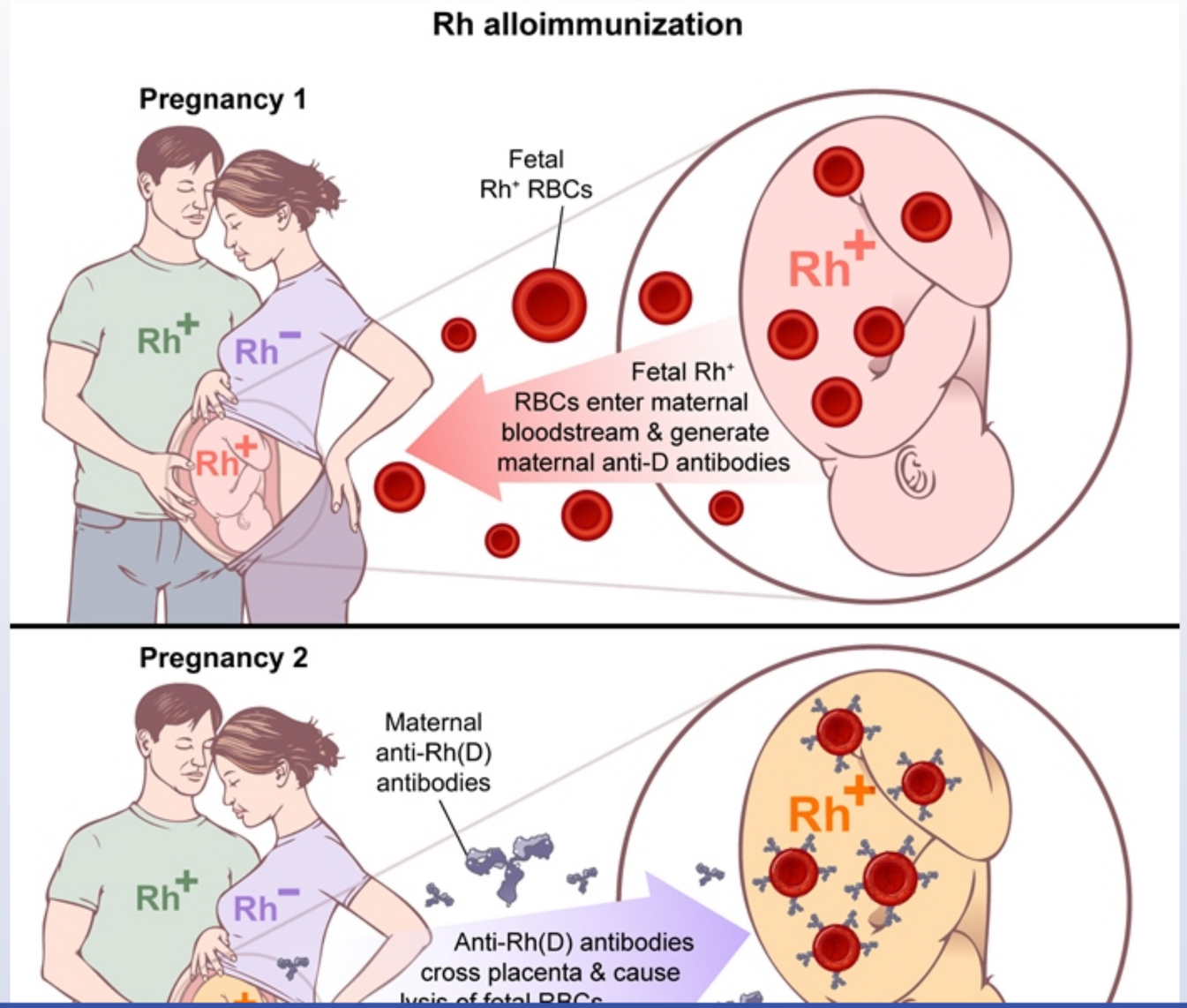
72%
Answered correctly

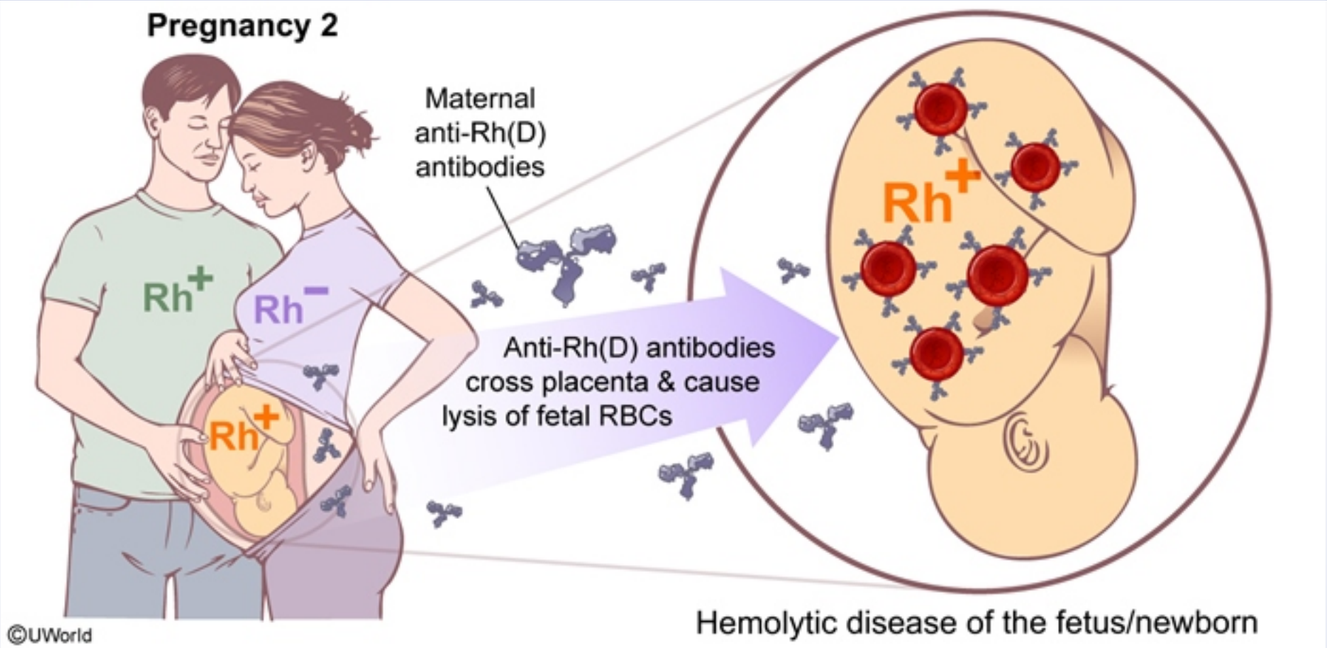
02 secs
Time Spent

07/01/2020
Last Updated

Explanation




Rh alloimmunization
Pregnancy 1
Fetal
Rh⁺ RBCs
Rh+
Rh−
Rh+
Rh+
Fetal Rh⁺
RBCs enter maternal
bloodstream & generate
maternal anti-D antibodies
Pregnancy 2
Maternal
anti-Rh(D)
antibodies
Rh+
Rh−
Rh+
Anti-Rh(D) antibodies
cross placenta & cause



Rhesus (Rh) antigens are a group of nonglycosylated, transmembrane proteins found on the surface of red blood cells. The D antigen is the most immunogenic of the group and is present on the erythrocytes of Rh-positive individuals. When an Rh-negative mother becomes pregnant with an Rh-positive fetus, fetal red blood cells can enter the maternal circulation and elicit a maternal antibody response with the formation of memory B lymphocytes (**Rh alloimmunization**). After Rh alloimmunization occurs, subsequent pregnancies with Rh-positive fetuses will be at risk for **hemolytic disease of the newborn**.

To avoid maternal Rh alloimmunization, Rh-negative mothers must be prevented from mounting an immune response against the D antigen. **Anti-Rh(D) immunoglobulin** is a polyclonal antibody product consisting of **IgG anti-D** antibodies collected from pooled donor plasma. It is **administered to Rh-negative women** during gestation and in the immediate postpartum period. Once given, anti-Rh(D) antibodies bind to Rh-positive fetal erythrocytes that enter the maternal circulation, preventing their interaction with the maternal immune system by promoting sequestration and elimination in the mother's spleen (ie, the mononuclear phagocyte system).

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Although IgG antibodies can cross the placenta, anti-Rh(D) IgG antibodies do not cause significant transplacental fetal hemolysis because the amount of antibody administered is negligible compared with the amount produced in a typical immune hemolytic reaction.

(Choice A) IgA is primarily a mucosal antibody. Patients with IgA deficiency can have an anaphylactic reaction during the administration of intravenous immunoglobulin.

(Choice B) IgD is present in very low concentrations in the blood and is typically coexpressed with IgM as a B-cell membrane receptor.

(Choice C) IgE plays a significant role in allergic responses and in the immune response to parasitic infections.

(Choice E) Multivalent IgM antibodies are generally more effective than IgG antibodies at promoting agglutination of foreign antigens and activating complement, which would result in lysis of fetal erythrocytes in the maternal circulation. However, macrophages do not have receptors for IgM; therefore, anti-D IgM does not provide the same immunoprophylactic effect (eg, sequestration and clearance of Rh-positive erythrocytes) as anti-D IgG.

Educational objective:
Anti-Rh immunoglobulin consists of anti-D IgG antibodies that bind to Rh-positive fetal erythrocytes, promoting clearance by maternal reticuloendothelial macrophages and preventing maternal Rh sensitization. It is routinely administered to Rh-negative women during gestation and immediately postpartum.

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References

- Mechanisms of anti-D action in the prevention of hemolytic disease of the fetus and newborn.

Immunology	Hematology & Oncology	Rhesus alloimmunization
Subject	System	Topic

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Immunology	Hematology & Oncology	Rhesus alloimmunization
Subject	System	Topic

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A 28-year-old woman, gravida 2 para 2, brings her healthy 6-day-old girl to the office for her first well-baby checkup. The infant was born full-term, with a birth weight of 4.2 kg (9.3 lb) and a length of 51 cm (20 in). She was discharged from the nursery with no concerns. Physical examination is normal. The infant's blood type is A negative, whereas the mother's is B negative. High circulating levels of anti-A antibodies are found in the mother's blood. Hemolysis did not occur in the infant because these maternal antibodies are most likely of which class?

- A. IgA
- B. IgD
- C. IgE
- D. IgG
- E. IgM

Submit

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A. IgA (3%)
B. IgD (3%)
C. IgE (0%)
D. IgG (14%)
✓ E. IgM (78%)

Omitted
Correct answer
E

78%
Answered correctly

02 secs
Time Spent

04/16/2020
Last Updated

Explanation

RBC antibody screen		
Maternal blood group	**Maternal RBC antigens**	**Maternal serum antibodies**
A	A antigen	Anti-B (IgM)

RBC antibody screen		
Maternal blood group	**Maternal RBC antigens**	**Maternal serum antibodies**
A	A antigen	Anti-B (IgM)
B	B antigen	Anti-A (IgM)
AB	A and B antigen	None
O	None	Anti-A and Anti-B (IgM and IgG)

RBC = red blood cell.

Hemolytic disease of the fetus and newborn (HDFN) is caused by maternal anti-fetal erythrocyte IgG antibodies, which can cross the placenta and produce a type II (antibody-mediated) hypersensitivity response. With maternal blood types A or B, hemolysis (eg, erythrocyte destruction) does not occur because the maternal antibodies (anti-A or anti-B) are of the IgM type, which cannot cross the placenta. However, mothers with **blood type O** also produce **IgG** antibodies which can cause **hemolysis** in the fetus.

The association of a fetus with blood type A or B and a mother with blood type O occurs in approximately 15% of pregnancies; however, HDFN occurs in only 3% of these pregnancies due to variations in fetal ABO antigen expression. Unlike Rh disease, HDFN can occur with the **first pregnancy** because anti-A and anti-B antibodies are formed early in life from exposure to A- or B-like antigens present in foods, bacteria, and viruses.

(Choice A) IgA plays an important role in mucosal immunity and is found in high amounts in colostrum. The secretory IgA provided by the mother's breast milk coats the infant's intestinal mucosa and provides protection from ingested pathogens.

(Choice B) IgD is an immunoglobulin of unclear significance. It is often concurrently expressed with IgM on the membranes of B lymphocytes and is believed to act as a cell surface antigen receptor for those cells.

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(Choice C) IgE is the immunoglobulin most notably responsible for atopic diseases such as asthma, atopic dermatitis, and allergic rhinitis. It also plays a role in defense against helminth parasites.

(Choice D) IgG crosses the placenta and remains circulating in the bloodstream of infants, providing them with passive immunity for up to 6 months.

Educational objective:
With maternal blood types A or B, hemolytic disease of the fetus and newborn very rarely occurs because maternal antibodies (anti-A or anti-B) are of the IgM type and cannot cross the placenta. In contrast, mothers with blood type O also produce IgG antibodies (anti-A and anti-B), which can cross the placenta and cause fetal hemolysis.

References

- Haemolytic disease of fetus and newborn.

Immunology Hematology & Oncology Rhesus alloimmunization

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References

- Haemolytic disease of fetus and newborn.

Immunology	Hematology & Oncology	Rhesus alloimmunization
Subject	System	Topic

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A newborn girl is admitted to the neonatal intensive care unit with jaundice, hepatomegaly, and generalized edema. She was born by vaginal delivery to a 32-year-old woman, gravida 2, para 2, who received minimal prenatal care. The infant's laboratory results show a hemoglobin level of 6 g/dL and a positive direct Coombs test. A peripheral blood smear shows many nucleated erythrocytes. The infant has significant respiratory distress due to pleural effusions and ascites and dies soon after birth. Autopsy shows areas of extramedullary hematopoiesis in many tissues. Which of the following is the most likely cause of this patient's condition?

A. Abnormal hemoglobin polymerization

B. Absence of alpha globin chains

C. Erythrocyte opsonization by maternal antibodies

D. Glucose-6-phosphate dehydrogenase deficiency

E. Red blood cell lysis by fetal antibodies

Submit

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- A. Abnormal hemoglobin polymerization (2%)
- B. Absence of alpha globin chains (7%)
- ✓ C. Erythrocyte opsonization by maternal antibodies (76%)
- D. Glucose-6-phosphate dehydrogenase deficiency (2%)
- E. Red blood cell lysis by fetal antibodies (11%)

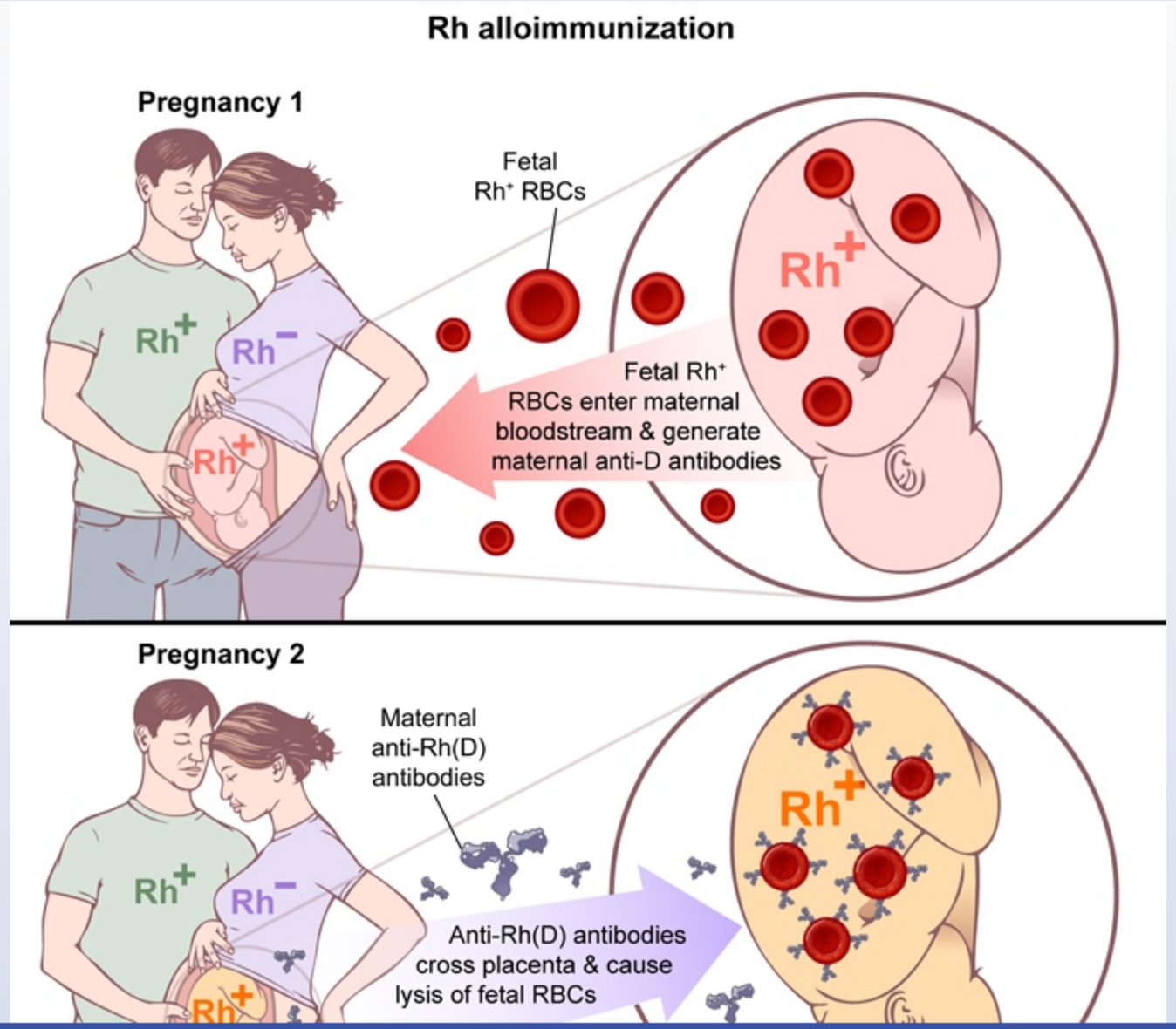
Omitted
Correct answer
C

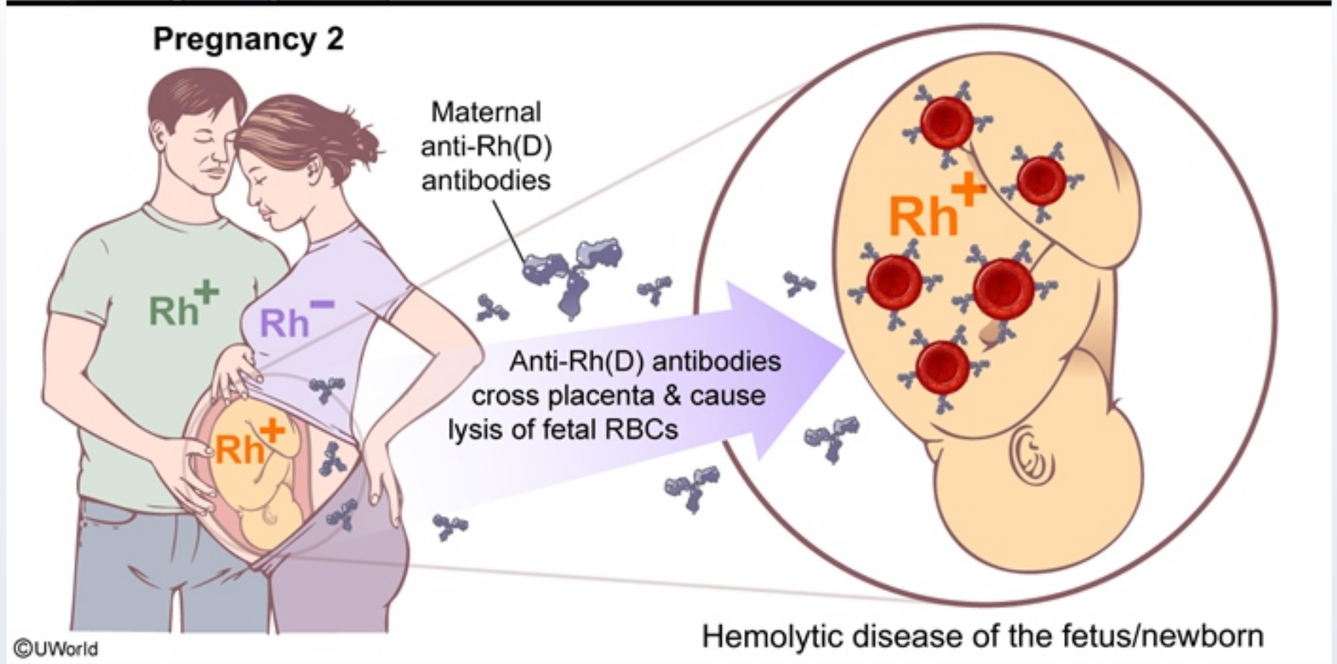
76%
Answered correctly

02 secs
Time Spent

02/18/2020
Last Updated

Explanation


Rh alloimmunization
Pregnancy 1
Fetal
Rh⁺ RBCs
Rh+
Rh−
Rh+
Rh+
Fetal Rh⁺
RBCs enter maternal
bloodstream & generate
maternal anti-D antibodies
Pregnancy 2
Maternal
anti-Rh(D)
antibodies
Rh+
Rh−
Rh+
Rh+
Anti-Rh(D) antibodies
cross placenta & cause
lysis of fetal RBCs



Hemolytic disease of the newborn (erythroblastosis fetalis) results from the destruction of fetal red blood cells by maternal antibodies directed against fetal erythrocyte antigens. These antibodies are **IgG antibodies**, the only class of antibody able to cross the placenta. Erythroblastosis fetalis is most commonly caused by Rhesus (Rh) incompatibility (particularly the D antigen).

Rh sensitization can occur in an **Rh(D)− mother** during pregnancy with an **Rh(D)+ fetus** due to small amounts of fetal blood crossing the placenta and entering the maternal circulation. These erythrocytes are viewed as foreign by the maternal immune system and induce the production of anti-Rh(D) IgG antibodies. In **subsequent pregnancies** with an Rh(D)+ fetus, these antibodies cross the placenta and opsonize fetal erythrocytes, causing hemolysis. This results in a positive direct Coombs test (indicating autoimmune hemolysis), profound **anemia, jaundice** (possibly leading to kernicterus), and generalized edema (**hydrops fetalis** due to accumulation of interstitial fluid). The severe anemia also stimulates release of immature, **nucleated erythrocytes** and leads to persistent **extramedullary hematopoiesis** in the liver, spleen, and other tissues (hepatosplenomegaly).

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(Choice A) Sickle cell anemia causes vasoocclusion due to abnormal hemoglobin polymerization. It is asymptomatic in the fetus/neonate due to high levels of fetal hemoglobin that are not replaced by hemoglobin S until age 3-12 months.

(Choice B) Fetuses with homozygous alpha-thalassemia (hemoglobin Barts) have no alpha globin chains and therefore form gamma-4 tetramers with very high oxygen affinity. The consequence is severe functional anemia and tissue hypoxia, which results in high-output heart failure and nonimmune hydrops fetalis (negative Coombs test).

(Choice D) Glucose-6-phosphate dehydrogenase deficiency can cause prolonged neonatal jaundice (beyond 2 weeks) due to increased erythrocyte breakdown and immaturity of the newborn liver. However, the associated anemia is rarely severe.

(Choice E) Infants are born with an immature immune system; their humoral defense during the first 6 months of life comes primarily from maternal circulating IgG that is received transplacentally prior to birth and from mucosal IgA received via breastfeeding. Therefore, fetal antibody-mediated red blood cell lysis is an unlikely etiology.

Educational objective:
Hemolytic disease of the newborn most commonly occurs from maternal sensitization to Rh antigens during a prior pregnancy with an Rh(D)+ fetus. In subsequent Rh(D)+ pregnancies, maternal anti-Rh(D) IgG antibodies cross the placenta and cause a severe autoimmune hemolytic anemia in the fetus and life-threatening hydrops fetalis.

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Hemolytic disease of the newborn most commonly occurs from maternal sensitization to Rh antigens during a prior pregnancy with an Rh(D)+ fetus. In subsequent Rh(D)+ pregnancies, maternal anti-Rh(D) IgG antibodies cross the placenta and cause a severe autoimmune hemolytic anemia in the fetus and life-threatening hydrops fetalis.

References

- Hemolytic disease of the fetus and newborn: managing the mother, fetus, and newborn.
- Etiology of non-immune hydrops fetalis: An update.

Immunology	Hematology & Oncology	Rhesus alloimmunization
Subject	System	Topic

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A 68-year-old man comes to the office for a follow-up appointment. He has a history of advanced melanoma that is unresectable and resistant to adjuvant regimens. The patient recently began receiving monoclonal antibody infusions for advanced melanoma. The monoclonal antibodies block a specific cell surface receptor found on T lymphocytes. As a result, T cells capable of recognizing tumor antigens have improved ability to destroy cancer cells. Which of the following cell surface receptors is most likely blocked by the treatment?

- A. CCR5
- B. CD4
- C. CD19
- D. CD28
- E. PD-1

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- A. CCR5 (13%)
- B. CD4 (17%)
- C. CD19 (6%)
- D. CD28 (25%)
- ✓ E. PD-1 (36%)

Omitted
Correct answer
E

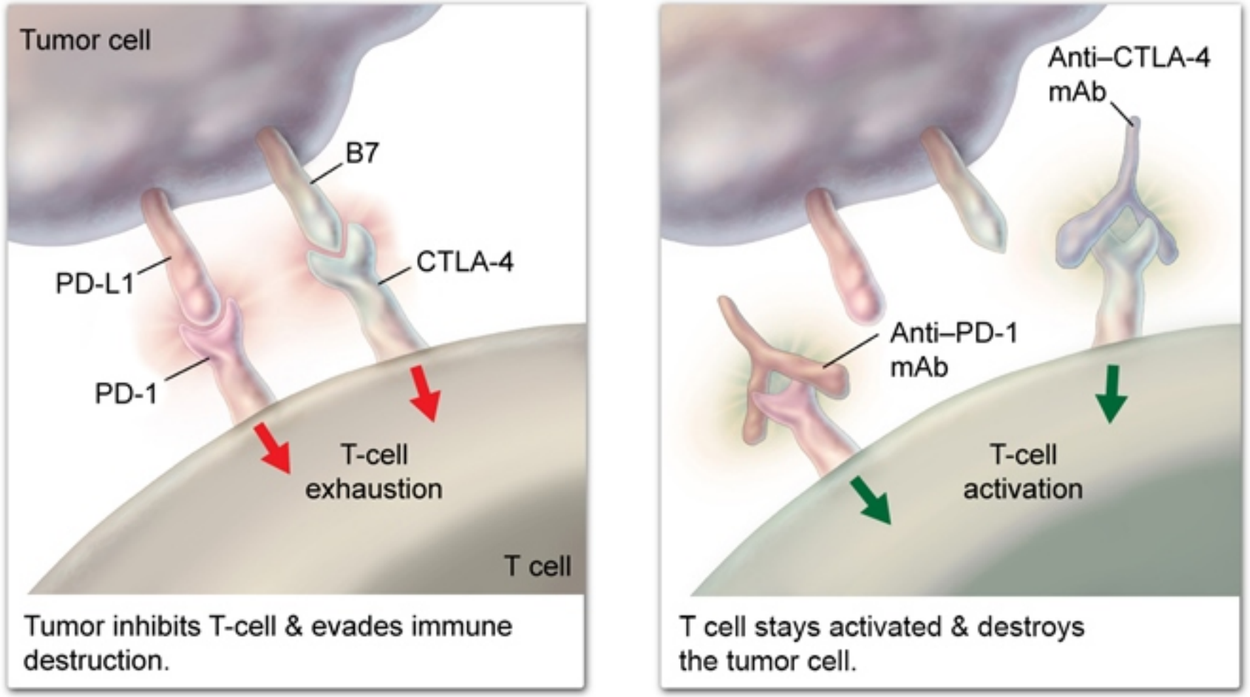
36%
Answered correctly

03 secs
Time Spent

04/12/2020
Last Updated

Explanation

Cancer immunotherapy: anti–PD-1 & anti–CTLA-4 antibodies



CTLA-4 = cytotoxic T-lymphocyte–associated protein 4; **mAb** = monoclonal antibody;
PD-1 = programmed death receptor-1; **PD-L1** = programmed death ligand-1.
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Oncogenesis generates proteins not found in healthy cells. Pieces of these proteins (**neoantigens**) are displayed on the cell surface and may be recognized by cytotoxic T-cells as "non-self" (leading to cellular apoptosis). However, neoplastic cells can blunt the cytotoxic T-cell response through a variety of mechanisms including the overexpression of **programmed death-ligand 1** (PD-L1), which binds to the PD-1 receptor on cytotoxic T cells and inhibits their ability to induce apoptosis (T-cell exhaustion).

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Treatment with **monoclonal antibodies** against PD-1 (eg, pembrolizumab, nivolumab) or PD-L1 (eg, atezolizumab) results in T-cell disinhibition and a restoration of the cytotoxic response (thereby increasing cancer cell apoptosis). Anti-PD-1 therapy is currently used in advanced melanoma, certain types of lung cancer, and renal cell carcinoma but is being explored for many other cancer types.

(Choices A and B) HIV uses chemokine coreceptor 5 (CCR5) to bind to CD4 cells. Antagonists to CCR5 have been developed for the management of patients with HIV. CCR5 also appears to promote CD4 cell anti-tumor responses, so antibodies blocking its function may downregulate immune-mediated tumor destruction. Blockade of CD4 itself would inhibit helper T-cell activation and reduce tumor cell destruction.

(Choice C) CD19 is expressed primarily on B cells (not T cells) and is important for B-cell signaling and activation.

(Choice D) CD28 is a T cell–specific surface protein that interacts with B7 on antigen-presenting cells, providing a costimulatory signal necessary for T-cell activation. Therefore, antibodies blocking CD28 would inhibit T-cell activation. CTLA-4 also binds to B7 but has an inhibitory function on activated T cells.

Educational objective:
The binding of programmed cell death protein 1 (PD-1) to one of its ligands (programmed death-ligand 1 [PD-L1]) downregulates the immune response by inhibiting cytotoxic T cells. Many types of cancers evade immunodetection by increasing expression of PD-L1 on their surface. Monoclonal antibodies against PD-1 upregulate the T-cell response and promote tumor cell apoptosis.

References

- Evolving concepts: immunity in oncology from targets to treatments.
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- The B7 family and cancer therapy: costimulation and coinhibition.
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- Cytotoxic T-lymphocyte–associated antigen-4.
- Rationale of anti-CD19 immunotherapy: an option to target autoreactive plasma cells in autoimmunity.
- CCR5 in cancer immunotherapy: more than an "attractive" receptor for T cells.

Immunology	Hematology & Oncology	Immunotherapy
Subject	System	Topic

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